American Journal of Obstetrics and Gynecology

VOL. 44 SEPTEMBER, 1942 No. 3

In Memoriam

HUGO EHRENFEST
1870-1942

HUGO EHRENFEST died July 24, 1942. Although he had in the past few years had occasional symptoms of angina, this had not incapacitated him from his duties as obstetrician and co-editor of the JOURNAL. After the usual busy morning at the hospital and in the office he went home to take his afternoon siesta and without arousing passed peacefully from slumber to death.

Born in Vienna 72 years ago, he took his doctor's degree at the University in that city in 1894. He served as assistant in Professor Schauta's obstetrical clinic at the Allgemeine Krankenhaus from 1896 to 1899. In 1900 he came to America and settled in St. Louis, where his friend, the late George Gellhorn, well-known gynecologist, had preceded him by one year. He rapidly adapted himself to his new home, and in 1904 married Sophie Schwab, a member of an old St. Louis family, who with two sons and a daughter survive him. He rapidly became a leader in his specialty. In 1904 he was appointed assistant professor of obstetrics and gynecology at St. Louis University and in 1907 was elected a Fellow of the American Gynecological Society, serving as vice-president of this Society in 1921. He was also a member of the Central Association of Obstetricians and Gynecologists and the St. Louis Gynecological Society. From 1904 to 1920 he taught at St. Louis University School of Medicine, being head of his department for a large part of that period. In 1922 he became associate professor of obstetrics and gynecology at Washington University School of Medicine, where he was engaged in teaching until the time of his death. From 1936 on he held the title of Professor Emeritus. His hospital appointments were at the Jewish Hospital, St. Louis Maternity Hospital, and Barnes Hospital.

From 1908 until he retired as consultant in 1936, he directed the organization and policies of the division of obstetrics and gynecology at the Jewish Hospital and was largely instrumental in setting up the standards at that institution.

His contributions to the literature of our specialty were numerous. He wrote chapters in Peterson's "Textbook of Obstetrics," in Davis' "Obstetrics and Gynecology" in Nelson's "Loose-Leaf Practice of Medicine," and in Crossen's "Diseases of Women," besides writing many journal articles. In 1925 he translated and prepared an American edition of Koehler's "Therapy of Puerperal Fever."

As a scientist Ehrenfest concentrated his interest in the field of obstetrics. He contributed much to the technique of pelvimetry and to the knowledge of the diseases complicating pregnancy, but his most outstanding work was his volume on "Birth Injuries of the Child," contributed to the Appleton Monograph series (1922). He was literally an encyclopedia of knowledge on almost every subject in obstetrics. It was this painstaking and comprehensive investigation combined with an ability to analyze and correlate his data that has made the monograph on birth injuries the outstanding work on this subject.

His teaching experience dated back to 1904. During the 16 years he served as professor at St. Louis University and the 20 years he was teaching at Washington University, he instructed many students of medicine. His influence in the development of sane, conservative obstetrics in this large group was most beneficial. He scrupulously avoided fads and opposed the indiscriminate use of twilight sleep, cesarean section, Dührssen incisions, etc. "Meddlesome midwifery" was in his opinion the cause of the persistently high maternal and infant mortality, and in the well-known Conference on Child Welfare held in President Hoover's administration, he was chairman of the special committee dealing with this subject. He was an unusually effective teacher not merely because of the clear analytical method of expressing his ideas but because of the droll and amusing way in which he embellished them from the wealth of his personal experience.

Even more important than his contributions as scientist and teacher was his work as editor. With amazing rapidity after coming to this country, he acquired a mastery of the English language and correct diction. It was not long before he was correcting our use of English instead of our correcting his. As one of the editors of the *Interstate Medical Journal,* and since 1920 as associate editor and later as co-editor of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, he spent a lifetime in correcting and clarifying innumerable scientific articles contributed to these journals. The number of grammatical errors in our papers that he has picked up and deleted are legion. We should all of us be grateful to him for having helped us in this thankless job of making our contributions more intelligible and less wordy.

To those who knew Hugo Ehrenfest intimately, he was a man of many accomplishments and a genial personality. The charm of Vienna, where so many of us spent happy and profitable days in the past, was mirrored in his activities. Music was his diversion. He spent many hours at the piano and often had the leading members of the Symphony Orchestra at his home. Simple and unassuming, he had a keen sense of humor and a spirit of kindliness toward all. We shall long miss his presence at our meetings.

Fred. J. Taussig, M.D.

A TRIBUTE

Hugo Ehrenfest was my valued friend and associate in the Editorship of the Journal since its founding in 1920. Among other tasks he developed the important Department of Abstracts and Reviews, and conducted it with unfailing skill because of his wide reading and his knowledge of the world's medical literature.

The many trials and tribulations connected with the editorial conduct of a widely circulated journal with its host of contributors, afforded many occasions on which his advice and suggestions were of utmost value and assistance.

Moreover by his lovable personality, his modesty, his cheerfulness, his always ready spirit of cooperation and his kindly disposition, Dr. Ehrenfest endeared himself to all the members of the Editorial and Publication Staffs of the Journal, who mourn deeply his sudden and untimely death. His many good deeds, his unselfish character, his sympathetic attitude, will all contribute to the happy memories and the esteem in which he was held by his many personal friends and associates. His loss is keenly felt.

George W. Kosmak, M.D.

Original Communications

THE PULSE AND RESPIRATORY RATES DURING LABOR AS A GUIDE TO THE ONSET OF CARDIAC FAILURE IN WOMEN WITH RHEUMATIC HEART DISEASE

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IN A previously reported study[1] of the pulse and respiratory variations of 180 normal women during labor, it was observed that the pulse and respirations remained practically unchanged throughout the first stage of labor. With the advent of bearing down efforts in the second stage of labor 4 per cent of patients showed a rise of the pulse rate to above 110 per minute with respirations of not over 24 per minute. Such elevations were considered as established only when they persisted for at least forty-five minutes. Thirteen per cent showed a rise in the respiratory rate to above 24 per minute with the pulse rate not over 110, and 7 per cent showed a rise of both pulse and respiratory rates above these values. The levels of 110 and 24 were chosen arbitrarily since a large percentage of patients approached or reached these values but relatively few exceeded them. Prolonged labor and prolonged second stage were found to predispose to such rises but no definite influence of analgesia or of the particular analgesic used could be observed.

We have extended these studies to women with rheumatic heart disease to note if their pulse and respiratory variations during labor differed in any way from those of normal women so as to give a warning of the approach of serious cardiac insufficiency. The 200 patients studied were first seen in the ante-partum clinic at various stages of their pregnancy. The diagnosis of the particular form of heart disease was made at this time and sometimes was amended as later observations seemed to indicate. The patients were classified as to their functional capacity (Class 1, 2, 3, or 4) according to the criteria of the New York Heart Association, and as they were followed progressively in the ante-partum clinic, this diagnosis was changed as indications seemed to warrant.

At the onset of labor or as soon thereafter as the patient was admitted to the hospital, the pulse and respirations were counted every fifteen minutes between pains and charts made of this similar to those appear-

ing in Figs. 1 to 5. The chart was continued up to the time of delivery or the onset of any operative procedure which involved the administration of an anesthetic. Analgesia was used as indicated but the barbiturates and scopolamine were avoided because of their tendency to produce restlessness and excitement. Open drop ether or local anesthesia was most commonly used for delivery.

This group of 200 patients included practically all of those with rheumatic heart disease who were delivered during the period when this study was being undertaken. Only a few cases were omitted because of the short duration of the first stage of labor or of the short period of observation in the hospital during this stage, but none of these cases were severe cardiacs. No cesarean section was performed during this period for the primary indication of rheumatic heart disease. Except for one case of pyeloureteritis (Case 8) and one of upper respiratory infection (Case 5), none of the patients included in this study had medical complications apart from the cardiac condition, that is, there was no unexplained fever, thyroid disease, true marked anemia, et cetera.

The various anatomic lesions included in the diagnoses of this group and the ante-partum diagnosis of cardiac functional capacity appear in Table I which also indicates the occurrence of intra-partum and post-partum cardiac failure. As is usual in observing cardiac disease during pregnancy, mitral stenosis is by far the most frequent valvular lesion

TABLE I. ANTE-PARTUM ANATOMIC AND FUNCTIONAL CLASSIFICATION OF CASES

LESION	CLASS 1	CLASS 2	CLASS 3	CLASS 4	TOTAL
MS, MI	62	84 ●	13 ○○	2	161
MS, MI, AI	10 ○	17	4 ●○	0	31
MS, MI, AI, AS	0	6	0	0	6
AI, AS	0	2	0	0	2
Total	72	109	17	2	200
Incidence of intra-partum and post-partum failure	1.3%	0.9%	24%	0	

Each case developing failure intra partum ○; post partum ●

both among the group as a whole and among the more serious cases. The relatively large number of Class 2 patients may be accounted for by the fact that the diagnosis was in most instances made during the last trimester of pregnancy. Had the functional classification been made earlier in pregnancy, there might have been more in Class 1 and fewer in the Class 2 group. The incidence of severe failure in the Class 3 group was 24 per cent, but in the other groups was small. This is in accordance with previous experiences[2] which tend to show that patients with Class 1 and 2 functional capacity rarely develop severe failure during pregnancy. The two cases who were Class 4 during pregnancy and yet after treatment improved and went through labor without severe failure, are truly remarkable examples of the possibilities under proper medical management. They are described later in detail.

Table II includes all patients whose pulse rate rose to above 110 and whose respiratory rate rose to above 24 during the first stage of labor, and remained so for at least forty-five minutes. This group consists of six Class 3 patients, three Class 2 and one Class 1. A careful review of the histories indicated that two of the Class 2 patients probably should have been diagnosed as Class 8.

Three of the patients developed severe cardiac failure (Class 4) for the first time in their life during the first stage of labor.

TABLE II. PATIENTS WITH PULSE RATE ABOVE 110 PER MINUTE AND RESPIRATORY RATE ABOVE 24 PER MINUTE DURING FIRST STAGE OF LABOR

CASE	FUNCTIONAL CAPACITY			DURATION OF LABOR HOURS	PULSE	RESP.	DIGITALIS	DELIVERY	COMMENT
	AP.*	IP.	PP.						
1	3	4	3	11	120	26	+	Forceps	Failure intra-partum
2	1	4	3	14	140	40	+	Forceps	Failure intra-partum
3	3	3	3	8	130	30	+	Forceps	
4	2	3	3	38	120	28	+	Forceps	
5	3	3	3	11	120	30	+	Spont.	
6	3	3	3	28	140	30	+	Cesarean	
7	3	3	4	15	120	30	+	Forceps	Failure 10 hr. post-partum
8	2	3	3	13	140	28	+	Breech	
9	3	4	3	31	120	40	+	Forceps	Failure intra-partum
10	2	3	4	44	120	28	0	Spont.	Failure 6 hr. post-partum

Figures for pulse and respirations are the maximum rate found for three or more consecutive counts during the first stage of labor.

*AP., ante partum. IP., intra partum. PP., post partum.

Case 2 had been diagnosed as Class 1 ante partum and had spontaneous rupture of the membranes at home very early in labor, after which she hurriedly dressed, packed, ran down five flights of stairs and came to the hospital in a taxicab. On admission her pulse was 140 and respirations 40. Soon thereafter she began to feel a choking sensation and developed pulmonary edema. She was treated with morphine, atropine, oxygen, and digitalis. Labor continued and she was delivered after a fourteen-hour labor, forceps being used to eliminate the second stage. This patient made an uneventful recovery and left the hospital in such condition that she has subsequently been diagnosed as Class 1 in the cardiac clinic. In her previous pregnancy she had been admitted for rest and digitalization prior to term, was allowed to go into labor spontaneously, and was delivered by forceps at the end of the first stage. During that confinement there was no evidence of severe cardiac failure.

Two patients who had been diagnosed as Class 3 during the last trimester, developed severe failure with basal râles, venous engorgement and cyanosis during the first stage of labor.

One of these patients, Case 1, had an attack of nocturnal dyspnea at the seventh month of her pregnancy and following this she showed more shortness of breath on exertion than previously and was placed in functional Class 3. She went into labor spontaneously at term. After two hours (nine hours before delivery), the pulse was 120 and respirations 24. Two hours prior to delivery the pulse was 112 and the respirations 26. One-half hour later pulmonary edema developed and was treated with morphine, atropine, digitalis, and oxygen. One hour later the patient was delivered by forceps at the end of the first stage, labor having lasted eleven hours. She made an uneventful recovery. The other patient, Case 9, a part of whose chart is shown as Fig. 1, showed a

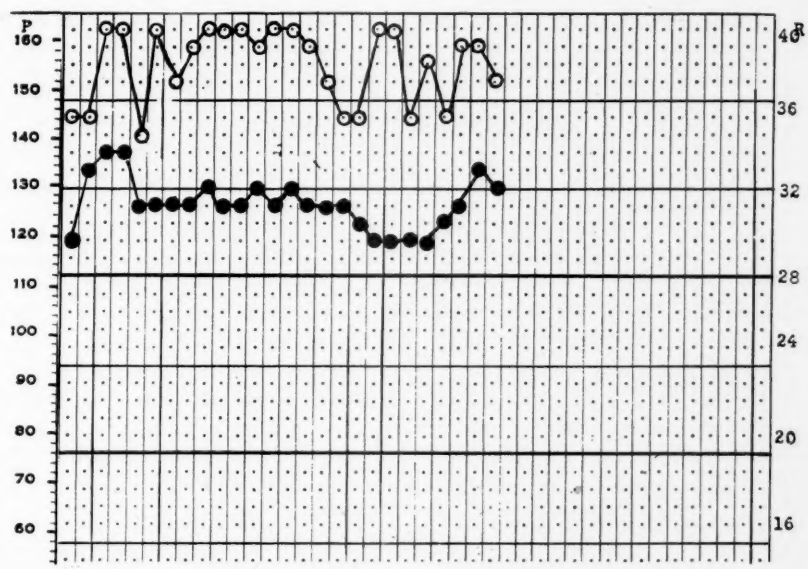

Fig. 1.—Case 9, 36-year-old primigravida, Class 3 ante-partum. Pulse (●) and respirations (○) every fifteen minutes during the last six and one-half hours of the first stage of labor at term. Total labor thirty-one hours. Pulse rate 110 and respiratory rate above 24 for twenty-two hours before failure. Developed cardiac failure. Given digitalis and delivered by forceps at full cervical dilatation. Satisfactory recovery. P, pulse; R, respiration.

pulse of 120 to 140 and respirations of 36 to 40 after four hours of labor (twenty-seven hours before delivery). Both rates continued high and after twenty-six hours of labor (five hours before delivery), the patient became restless and developed cyanosis, pulmonary râles, and more marked dyspnea. She was treated as was the previous patient and was delivered at the end of the first stage by midforceps after thirty-one hours of labor. The respiratory rate was increased for twenty-four hours post partum and the pulse for four days, but the patient made a satisfactory recovery.

Another Class 3 patient in this group, Case 6, continued in labor well digitalized for twenty-eight hours, during the last six hours of which both the pulse and respirations were above 110 and 24, respectively. A cesarean section was finally done because of cephalopelvic disproportion. This patient made an uneventful recovery.

Two patients without history of previous decompensation developed severe cardiac failure during the first twelve hours post partum.

One of these, Case 7, had been diagnosed Class 3 ante partum as early as the third month of pregnancy. She was given digitalis, followed in the clinic, and admitted ten days prior to the expected date of confinement for rest and further digitalization. Her labor lasted fifteen hours. The pulse was 120 and respirations 28 at the onset, and during the last six hours the pulse was above 120 and the respirations 30. The second stage was eliminated by forceps without excessive blood loss, and she left the operating room in good condition. She continued well until eight hours post partum when she was noted to be pale with a pulse of 140 and respirations of 20. The fundus was still well contracted and there had been no hemorrhage. At that time there were no pulmonary râles, but two hours later she developed pulmonary edema. She responded well to treatment and recovered. The other patient who developed failure post partum, Case 10, had been diagnosed as Class 2 at the sixth month of pregnancy. Her labor lasted forty-four hours without digitalis therapy. After nine hours (thirty-five hours before delivery), the pulse was 120 and respirations 22. After twelve hours the pulse was 100 and respirations 20, after twenty-four hours 110 and 24, after twenty-eight hours 108 and 26, after thirty-six hours 110 and 26, and after thirty-nine hours 120 and 26, respectively. The patient was allowed to continue in the second stage and delivered spontaneously. The pulse finally had risen to 126 and respirations to 30. She had a minimal blood loss and left the delivery room without evidence of pulmonary congestion. Six hours thereafter pulmonary râles, cyanosis, venous engorgement and dyspnea were noted, at which time the pulse was 104 and respirations 28. She responded to treatment, however, and made a satisfactory recovery.

All the remaining patients in Table II received digitalis before or during labor, all but one were delivered by forceps (except one breech presentation) and all did satisfactorily.

TABLE III. PATIENTS WITH PULSE RATE ABOVE 110 PER MINUTE AND RESPIRATORY RATE NOT ABOVE 24 DURING FIRST STAGE OF LABOR

CASE	FUNCTIONAL CAPACITY			DURATION OF LABOR HOURS	PULSE	RESP.	DIGITALIS	DELIVERY	COMMENT
	AP.*	IP.	PP.						
11	2	2	2	10	120	22	0	Spont.	Persistent tachycardia
12	2	2	2	27	120	20	0	Forceps	Persistent tachycardia
13	3	4	3	10	120	22	+	Forceps	Failure intra partum
14	2	2	2	9	120	24	0	Spont.	
15	1	1	1	6	120	22	0	Spont.	Bearing down early
16	3	3	3	9	120	24	+	Forceps	
17	2	2	2	10	120	24	0	Forceps	Bearing down early

Figures for pulse and respirations are the maximum rate found for three or more consecutive counts during the first stage of labor.

*AP., ante partum. IP., intra partum. PP., post partum.

Table III includes all patients whose pulse rose to over 110 but whose respirations did not exceed 24 during the first stage of labor.

One Class 3 patient, Case 13, who had never previously decompensated, failed intra partum. Her chart is shown as Fig. 2. The pulse was found to be 120 and the respirations 22 after six hours of labor. Two hours later, without change in pulse or respiration, she developed basal râles, venous engorgement, and cyanosis. She improved after receiving morphine, oxygen, and digitalis, and forceps delivery was performed at full cervical dilatation one hour later after ten hours of labor. The post-partum course was satisfactory. The other Class 3

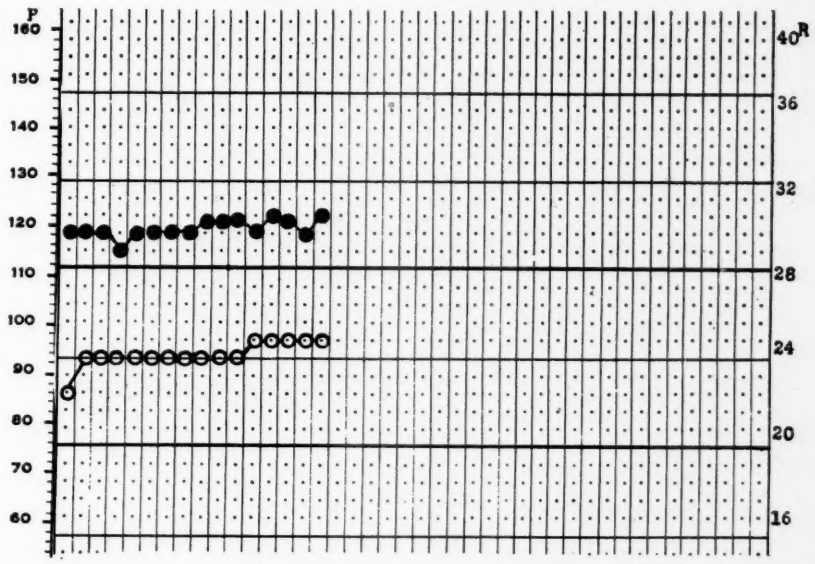

Fig. 2.—Case 13, 25-year-old primigravida, Class 3 ante partum. Pulse (●) and respirations (○) every fifteen minutes during the last four hours of the first stage of labor at term. Total labor ten hours. Earliest recordings two hours before failure show pulse rate above 110, but respiratory rate is not above 24. Developed cardiac failure one hour before delivery. Given digitalis and delivered by forceps at full cervical dilatation. Satisfactory recovery.

patient in Table III, Case 16, showed a pulse of 120 and respirations of 24 eight hours prior to delivery. She received digitalis and was delivered by forceps at full cervical dilatation after a nine-hour labor. The pulse rose to 128 but the respirations did not exceed 24. There was no serious cardiac failure. The remaining patients in this table were either Class 1 or 2. They did not receive digitalis and all came through without serious cardiac difficulty. Two were delivered by forceps and three delivered spontaneously. Two were bearing down early which may have caused the tachycardia. One of the latter patients displayed a persistent unexplained tachycardia in both her pregnancies (Cases 11 and 12). It was considered as probably due to apprehension.

Table IV includes all patients whose respiratory rate rose above 24 per minute but whose pulse rate did not exceed 110 per minute during the

TABLE IV. PATIENTS WITH RESPIRATORY RATE ABOVE 24 PER MINUTE AND PULSE RATE NOT ABOVE 110 DURING FIRST STAGE OF LABOR

CASE	FUNCTIONAL CAPACITY			DURATION OF LABOR HOURS	PULSE	RESP.	DIGITALIS	DELIVERY	COMMENT
	AP.*	IP.	PP.						
18	2	2	2	22	90	32	0	Forceps	Prolonged second stage
19	2	2	2	8	90	30	0	Spont.	Variable respiratory rate
20	1	1	1	12	80	30	0	Spont.	Bearing down early
21	2	2	2	15	90	30	0	Spont.	Bearing down early
22	2	2	2	14	90	28	0	Spont.	
23	2	2	2	5	90	36	0	Spont.	
24	2	2	2	12	90	26	0	Spont.	
25	2	2	2	6	100	30	0	Spont.	
26	3	3	3	20	90	40	+	Forceps	
27	2	2	2	11	80	40	0	Spont.	
28	2	2	2	13	80	26	0	Forceps	
29	2	2	2	48	106	30	0	Forceps	Prolonged second stage

Figures for pulse and respirations are the maximum rate found for three or more consecutive counts during the first stage of labor.

*AP., ante partum. IP., intra partum. PP., post partum.

first stage of labor. There was no instance of failure in this group of 12 patients.

There was one Class 3 patient, Case 26, whose chart during labor showed a maximum pulse of 90 and respirations of 40 thirteen hours prior to delivery. She received digitalis, was delivered by forceps at full cervical dilatation after twenty hours of labor, and showed no evidence of severe failure. The remaining patients were either Class 1 or 2 and did not receive digitalis. Three were delivered by forceps because of prolonged second stage; the remainder delivered spontaneously. Two of these patients were bearing down early, which may have caused the rapid respirations. One, Case 21, whose chart is shown in Fig. 3, was definitely hysterical with panting type of respirations.

Of the remaining 171 patients of the series none had pulse or respiratory rates above the critical levels during the first stage of labor and no instance of intra-partum or post-partum cardiac failure was encountered. Two of these patients were diagnosed as Class 4 ante partum. Eight were diagnosed Class 3, 92 were Class 2, and 69 were Class 1.

Tables V, VI, and VII pertain to elevation of the pulse and respiratory rates during the second stage of labor. It is evident from examination of these tables that most patients included in the previous tables showing pulse or respiratory elevation during the first stage of labor continued to show this during the second stage. All the new cases in Tables V, VI, and VII were Class 1 or 2 and no serious cardiac failure was encountered in any of these. Seven and one-half per cent of all patients

showed elevation of both pulse and respirations above the critical levels during the second stage of labor. Six and one-half per cent showed elevation of the pulse alone, and 15 per cent, elevation of the respirations

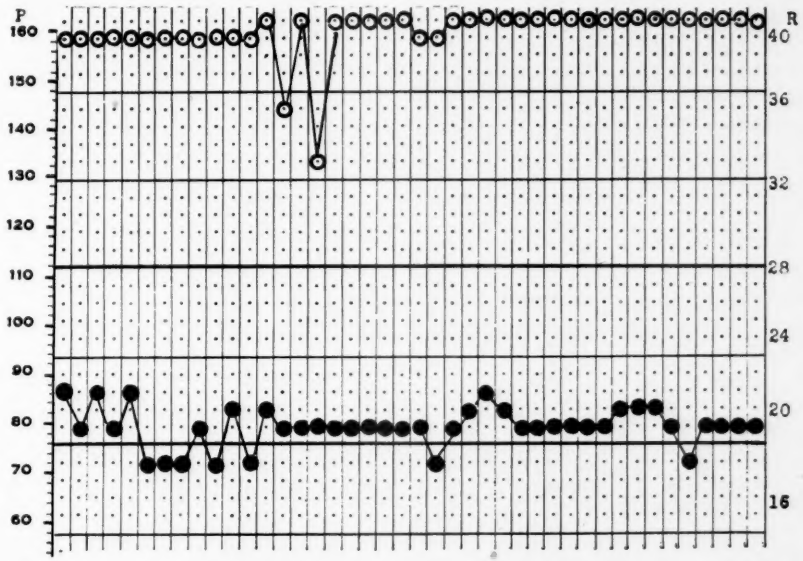

Fig. 3.—Case 27, 31-year-old para iii, gravida iv; Class 2 ante partum. Pulse (●) and respirations (○) every fifteen minutes during the last ten hours of the first stage of labor at term. Total labor eleven hours. Respiratory rate 40 practically throughout labor, although pulse rate was only slightly elevated. No digitalis, normal spontaneous delivery. No cardiac embarrassment during labor or post partum.

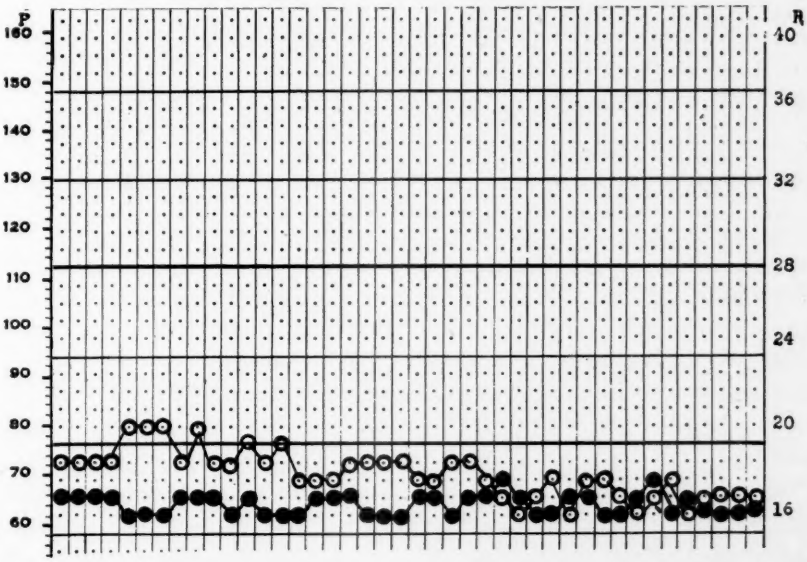

Fig. 4.—Pulse (●) and respirations (○) every fifteen minutes during the last ten and one-half hours of the first stage of labor at term. A 36-year-old primigravida had cardiac failure in the last trimester with recovery. Pulse rate below 110 and respiratory rate below 24 throughout labor. Total labor fifteen hours. Digitalis, forceps delivery at full cervical dilatation. No serious cardiac embarrassment intra partum or post partum.

alone. There is a striking similarity between these figures and the percentages obtained in the study of women with normal hearts, as stated in the introductory paragraph.

This series also included the two Class 4 patients previously mentioned who first appeared in the clinic during the seventh month of pregnancy, in a state of severe cardiac failure for the first time in their life history. Both patients improved with bed rest, digitalis, fluid and salt restriction, and continued in the hospital until they went into labor spontaneously, there being no additional obstetric complications. These cases do not appear in the tables of patients with elevated pulse and respirations because the pulse and respiratory counts did not rise above 110 and 24,

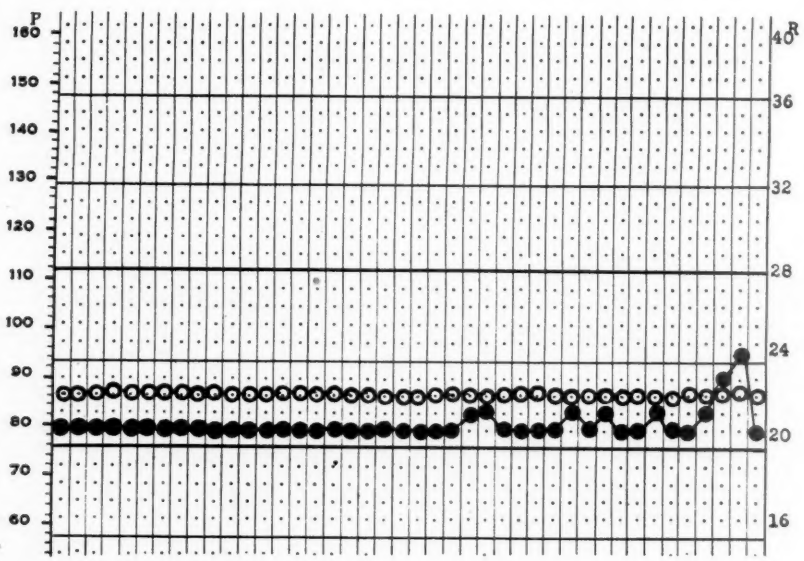

Fig. 5.—Pulse (●) and respirations (○) every fifteen minutes during the last ten and one-half hours of the first stage of labor at term. A 29-year-old primigravida, Class 2 ante partum. Total labor thirty-nine hours. No digitalis, normal spontaneous delivery. No cardiac embarrassment during labor or post partum.

respectively, during labor. Fig. 4 shows the chart of one of these patients who had persistent auricular fibrillation. Forceps delivery was performed at full cervical dilatation in this case and spontaneous delivery occurred soon after full dilatation in the other. The post-partum course was satisfactory in both instances. There were no other instances of ante-partum cardiac failure in the 200 patients studied.

Certain comments seem in order on the duration of labor in these patients. In the 200 cases studied, there were 26 with labor of over thirty hours' duration, the longest eighty-three hours. The pulse and respiratory rates were elevated above the critical levels during the first stage of labor in only 3 of these. Two of them, both Class 3 cases (9 and

10), have been previously discussed when considering Table II. The first developed severe failure during the first stage of labor, and the second, six hours after delivery. Both gave early evidence of severe heart strain in the elevation of pulse and respirations. A third patient with prolonged labor, Case 4, also gave early evidence of heart strain by the elevated pulse and respiratory rates. She was digitalized and delivered at full cervical dilatation after thirty-eight hours of labor. She came through without serious failure in spite of the fact that the pulse rose to 120 and the respirations to 28 twenty-four hours before delivery and remained at this level or higher.

Case 29, who was Class 2 ante partum and whose labor lasted forty-eight hours, showed a maximum respiratory rate during the first stage of 30, but the pulse rate was only 106. She did not receive digitalis, and was delivered by forceps after a prolonged second stage without any serious cardiac failure having arisen.

That prolonged labor does not necessarily lead to increased pulse and respirations has been previously demonstrated in normals, but Fig. 5 shows the chart of a Class 2 cardiac patient who delivered spontaneously after a thirty-nine-hour labor without digitalis. The pulse and respirations remained at normal levels and no failure ensued, this being typical of the majority of the 26 cases with prolonged labor.

Table VIII shows the type of delivery and the incidence of digitalis administration according to the various functional classes. The incidence of forceps delivery and digitalis administration naturally increases with decreasing functional capacity.

TABLE V. PATIENTS WITH PULSE RATE ABOVE 110 PER MINUTE AND RESPIRATORY RATE ABOVE 24 PER MINUTE DURING SECOND STAGE OF LABOR

CASE	FUNCTIONAL CAPACITY			DURATION OF LABOR HOURS	SECOND STAGE		DIGITALIS	DELIVERY	FIRST STAGE OF LABOR		COMMENT
	AP.*	IP.	PP.		PULSE	RESP.			PULSE	RESP.	
1	3	4	3	11	120	40	+	Forceps	120	26	See Table II
2	1	4	3	14	140	40	+	Forceps	140	40	See Table II
3	3	3	3	8	130	30	+	Forceps	130	30	See Table II
4	2	3	3	38	130	38	+	Forceps	120	28	See Table II
5	3	3	3	11	120	26	+	Spont.	120	30	See Table II
7	3	3	4	15	120	28	+	Forceps	120	30	See Table II
8	2	3	3	13	120	28	+	Breech	140	28	See Table II
9	3	4	3	31	130	40	+	Forceps	120	40	See Table II
10	2	3	4	44	120	28	0	Spont.	120	28	See Table II
30	1	1	1	6	120	30	0	Spont.	80	22	
31	1	1	1	9	120	28	0	Spont.	80	18	
32	2	2	2	7	120	30	0	Spont.	80	22	
33	2	2	2	9	140	28	0	Spont.	100	24	
34	2	2	2	7	112	26	0	Spont.	100	24	
35	2	2	2	12	120	28	0	Spont.	100	24	

Figures for pulse and respirations are the maximum rate found for three or more consecutive counts.

*AP., ante partum. IP., intra partum. PP., post partum.

TABLE VI. PATIENTS WITH PULSE RATE ABOVE 110 PER MINUTE AND RESPIRATORY RATE NOT ABOVE 24 DURING SECOND STAGE OF LABOR

CASE	FUNCTIONAL CAPACITY			DURATION OF LABOR HOURS	SECOND STAGE		DIGITALIS	DELIVERY	FIRST STAGE OF LABOR		COMMENT
	AP.*	IP.	PP.		PULSE	RESP.			PULSE	RESP.	
11	2	2	2	10	130	20	0	Spont.	120	22	See Table III
12	2	2	2	27	120	24	0	Forceps	120	20	See Table III
13	3	4	3	10	120	22	+	Forceps	120	22	See Table III
16	3	3	3	9	120	24	+	Forceps	120	24	See Table III
17	2	2	2	10	120	24	0	Forceps	120	24	See Table III
36	1	1	1	41	120	22	0	Spont.	100	22	
37	1	1	1	15	130	22	0	Spont.	102	22	
38	2	2	2	22	120	24	0	Forceps	100	22	
39	2	2	2	71	120	22	+	Forceps	80	20	
40	1	1	1	21	120	24	0	Spont.	100	20	
41	2	2	2	2	120	24	0	Forceps	80	20	
42	2	2	2	49	130	24	0	Forceps	100	20	
43	1	1	1	39	120	24	0	Spont.	90	22	

Figures for pulse and respirations are the maximum rate found for three or more consecutive counts.

*AP., ante partum. IP., intra partum. PP., post partum.

TABLE VII. PATIENTS WITH RESPIRATORY RATE ABOVE 24 PER MINUTE AND PULSE RATE NOT ABOVE 110 DURING SECOND STAGE OF LABOR

CASE	FUNCTIONAL CAPACITY			DURATION OF LABOR HOURS	SECOND STAGE		DIGITALIS	DELIVERY	FIRST STAGE OF LABOR		COMMENT
	AP.*	IP.	PP.		PULSE	RESP.			PULSE	RESP.	
18	2	2	2	22	100	32	0	Forceps	90	32	See Table IV
19	2	2	2	8	80	30	0	Spont.	90	30	See Table IV
20	1	1	1	12	90	30	0	Spont.	80	30	See Table IV
21	2	2	2	15	90	34	0	Spont.	90	30	See Table IV
22	2	2	2	14	80	28	0	Spont.	90	28	See Table IV
23	2	2	2	5	90	32	0	Spont.	90	36	See Table IV
24	2	2	2	12	90	26	0	Spont.	90	26	See Table IV
25	2	2	2	6	80	30	0	Spont.	100	30	See Table IV
26	3	3	3	20	100	30	+	Forceps	90	40	See Table IV
27	2	2	2	11	80	30	0	Spont.	80	40	See Table IV
28	2	2	2	13	80	26	0	Forceps	80	26	See Table IV
29	2	2	2	48	106	30	0	Forceps	106	30	See Table IV
44	1	1	1	12	100	30	0	Forceps	100	20	
45	1	1	1	19	110	28	0	Forceps	80	20	
46	1	1	1	50	100	28	0	Forceps	100	24	
47	1	1	1	5	100	40	0	Spont.	80	24	
48	2	2	2	9	110	28	0	Forceps	80	20	
49	1	1	1	10	80	30	0	Spont.	80	22	
50	2	2	2	14	110	40	+	Spont.	90	20	
51	2	2	2	5	80	30	0	Spont.	90	20	
52	1	1	1	22	80	30	0	Spont.	80	20	
53	1	1	1	10	80	28	0	Spont.	80	22	
54	1	1	1	11	100	28	0	Spont.	80	20	
55	2	2	2	31	80	30	0	Forceps	80	22	
56	1	1	1	5	100	30	0	Spont.	100	22	
57	2	2	2	30	100	30	0	Spont.	100	22	
58	2	2	2	7	70	30	0	Spont.	70	20	
59	2	2	2	28	90	30	0	Forceps	90	20	
60	1	1	1	42	80	30	0	Breech	80	20	
61	1	1	1	18	100	28	0	Forceps	100	22	

Figures for pulse and respirations are the maximum rate found for three or more consecutive counts.

*AP., ante partum. IP., intra partum. PP., post partum.

TABLE VIII. THE INCIDENCE OF FORCEPS DELIVERIES AND DIGITALIS ADMINISTRATION IN PATIENTS DIAGNOSED IN THE VARIOUS FUNCTIONAL CLASSES

	CLASS 1	CLASS 2	CLASS 3	CLASS 4
Total patients	72	109	17	2
Forceps	8	30	13	1
Digitalis	1	4	17	2

DISCUSSION

The pulse was above 110 and the respirations above 24 for more than forty-five minutes during the first stage of labor in all but one of the 6 cases that subsequently developed failure intra partum or post partum. In this case the pulse was persistently above 110 but the respirations were only 22. Five other cases had both the pulse and respirations above the critical figures yet did not develop failure either during or after labor. No significant differences could be found in their antecedent history or in their course during labor to account for this difference in the outcome. A careful review of the pulse and respiratory counts of these patients did not reveal any significant features which might have enabled us to predict that one patient was going to develop severe failure while another one was not. Even so, it seems evident that the presence of high pulse and respiratory counts is to be considered as a warning of impending failure even though this may not develop in all cases. Elevation of pulse alone may have a similar though less threatening significance as only one of 7 cases with this phenomenon developed failure.

We believe that more of these patients might have failed if the appearance of high pulse and respiratory counts had not been considered as a warning of the approach of serious cardiac insufficiency and led to the administration of digitalis and the shortening or elimination of the second stage of labor by the use of forceps. Sustained pulse and respiratory counts above the critical values call for prompt and adequate digitalization unless this has already been effected and for the elimination of the strain of the second stage as soon as feasible by the judicious use of forceps. Where only the pulse or the respiratory rate is abnormally elevated, less importance seems associated with elevation of the respiratory rate alone. No serious difficulty has been encountered in such cases, whereas the occurrence of elevation of the pulse alone preceding failure has been observed. There was no instance of serious cardiac embarrassment when the pulse and respirations remained normal throughout the first stage, regardless of levels attained during the second stage. It is interesting that the incidence of a rise of pulse and respirations above the critical levels during the second stage of labor in cardiac patients so closely parallels that previously observed in normal women. The significance of this is difficult to understand.

The data regarding length of labor suggest that even with an unusually prolonged labor, appropriate digitalization and elimination of

the second stage by forceps may in many cases help to avoid severe failure. In one of the instances of post-partum failure, Case 10, it seems that the cardiac strain might have been helped by digitalis and severe failure averted by judicious use of forceps. The dystocia labor, however, resolves itself primarily into an obstetric problem and should be treated accordingly as was done in Case 6 in which a cesarean section was performed because of failure of the head to engage.

All but one of these 200 rheumatic cardiac patients were delivered by the vaginal route. Disproportion was present in the patient delivered by cesarean section. There were 2 cases of ante-partum failure, 4 of intra-partum failure, 2 of post-partum failure, and 13 other Class 3 patients, and yet there was not a single maternal death. We would like to think that careful ante-partum care, functional evaluation, study of the pulse and respirations intra partum with appropriate and adequate digitalization, and judicious use of forceps to eliminate the strain of the second stage of labor are the important factors which made these results possible. The question of vaginal versus abdominal delivery in patients with serious rheumatic heart disease will be dealt with in a subsequent paper.

In view of the statement of Hamilton[3] and others that cardiac patients do not fail for the first time during labor, this group showing 4 such cases is of particular interest.

SUMMARY AND CONCLUSIONS

Two hundred cases of rheumatic heart disease complicating pregnancy are presented. The ante-partum functional capacity diagnoses were: 72 Class 1; 109 Class 2; 17 Class 3, and 2 class 4. One hundred ninety-nine were delivered by the vaginal route, and one was delivered by cesarean section because of disproportion. Intra-partum or post-partum cardiac failure occurred in 3 per cent of the 200 cases, none of whom had ever previously decompensated. The maternal mortality for the entire series was zero.

Elevation of the pulse rate above 110 per minute with elevation of the respiratory rate above 24 per minute, or such an elevation of the pulse rate alone during the first stage of labor preceded each instance of intra-partum or post-partum cardiac failure by sufficient time to afford a warning of its approach.

Ten patients (5 per cent) had elevation of pulse rate above 110 and respiratory rate above 24 during the first stage of labor. Three of these patients developed severe failure intra partum (Class 1, 3, 3 ante partum) and 2 post partum (Class 2, 3 ante partum).

Seven patients (3.5 per cent) had elevation of the pulse rate above 110 during the first stage of labor with the respiratory rate not above 24. One of these patients developed severe failure intra partum (Class 3 ante partum).

Twelve patients (6 per cent) had elevation of the respiratory rate above 24 during the first stage of labor with the pulse rate not above 110. None of these patients developed cardiac failure.

No instance of cardiac failure occurred in patients with both pulse and respirations below these critical levels during the first stage of labor regardless of the severity of the cardiac condition as indicated by the ante-partum functional classification.

During the second stage of labor 7.5 per cent of patients had both pulse and respirations above these critical levels, 6.5 per cent the pulse alone, and 15 per cent the respirations alone. No serious significance could be attached to such rises unless they were preceded by similar rises during the first stage of labor, and it is interesting that a similar percentage of normal women have been observed to show these types of pulse and respiratory reaction during the second stage of labor.

Proper management of the cardiac status may avoid severe cardiac failure even in the presence of unusually prolonged first stage of labor.

The successful management of patients with rheumatic heart disease during labor and post partum depends on various factors. Particular consideration should be given to the following:

Careful ante-partum care and cardiac functional evaluation.

Adequate ante-partum digitalization and elimination of the second stage of labor in all Class 3 patients.

Rapid adequate digitalization and elimination of the second stage of labor in any patient whose pulse and respirations exceed the figures which we have considered as a warning of the approach of serious cardiac insufficiency.

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Routine red blood counts and hemoglobin values were determined on 965 pregnant women between the twenty-sixth and the thirty-second week. A red blood count of 3.1 million and above and a hemoglobin of 8.29 Gm. (61 per cent Holden) and higher were taken as within the normal range. It was shown that age and parity have definite and deleterious effects on the blood of pregnant women. The anemia was most marked in the winter months. The morbidity in anemia was found to be lower than in healthy women. Children born of anemic women were found to be heavier. It was noticed than an inadequate ill-balanced diet was found in the cases of anemia.

William Berman.

TRUE BONE FORMATION IN THE FALLOPIAN TUBE

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WHENEVER a tissue is found in an abnormal location, two principal explanations can be considered: *heteroplasia,* i.e., a primary developmental anomaly, due to an error very early in cell division, or *metaplasia,* in the sense that the tissue cells have developed histogenetic potencies, which are not adequate to the particular location (A. Fischel). We know that, a priori, embryonal mesenchymal cells have the faculty to develop into different tissues, like connective tissue, muscle, cartilage, bone, etc. Into which of these the fetal mesenchymal cells develop depends mostly upon the organizing influences of neighboring tissues, particularly epithelium.

The old theory that, wherever bone tissue is found, it must have originated from cartilage or other tissues with normally osteogenic properties, is no longer tenable. Bone may be formed anywhere in the body by metaplasia of ordinary loose connective tissue (Maximow). It has been proved, e.g., that, in certain chronic inflammatory processes, the fibroblasts may acquire an almost embryonic totipotential character. Near deposits of old pus, detritus and calcium salt fibroblasts might develop into osteoblasts.

One may find such metaplastic bone formation as a consequence of chronic inflammation in muscle, heart, blood and lymph vessels, central nervous system and its membranes, lungs, liver and digestive system, urogenital tract, etc. In the Fallopian tubes such an occurrence is extremely rare. Though thousands of extirpated tubes are being examined histologically every year, no report of such a case could be found in a careful review of the American and English literature. Poscharissky,[1] who in 1905 made a survey of several hundred cases of "heteroplastic" bone formation in almost all organ systems, declares specifically that he knows of no such change in the tubes. In looking through old textbooks of pathology, however, I found it mentioned occasionally as a great rarity.[2-4]

The first detailed description of this interesting finding was published by Michaud[5] in 1908. Altogether eleven cases could be found in the world literature, one of which was published by an American author, L. W. Strong, from the Woman's Hospital, New York. But as this case appeared in a German periodical, the subject has as yet not been brought to the attention of the Anglo-American reader. In view of this fact, a brief survey of the cases reported so far is given in Table I.

TABLE 1

TABLE 1

NO.	AUTHOR	YEAR	AGE	PARA	MENSES	PREVIOUS HISTORY	GYNECOLOGIC FINDINGS			LOCALIZATION AND SIZE OF BONE FORMATION	PROBABLE ETIOLOGY
							UTERUS	OVARIES	TUBES		
1	Michaud[5]	1908	21	Virgin	Primary amenorrhea	Chlorosis. Hemoptoe at 7 years. Appendectomy at 20 years.	Infantile	Bilateral cystic tumors	Chronic salpingitis	Pars ampullaris on both sides	Tuberculosis ?
2	Emelijanow[6]	1911	46	?	?	?	?	Bilateral cystic tumors	Hydrosalpinx dextra	Pars isthmica of right tube. Pea-sized nodule	Unknown
3	Pozzi and Bender[7]	1912	31	0	Menarche at 17. Menses irregular, scant. Amenorrhea of 4 mo.	Gonitis at 13 years. Ovarian deficiency.	Infantile. Pedunculated myoma of egg size	Atrophic	Salpingitis nodosa	Pars interstitialis	Tuberculosis ?
4	Pozzi and Bender[7]	1912	34	i	Menarche at 15	Irrelevant	Normal	Small cystic	Salpingitis purulenta	Pars interstitialis. Hazelnut-sized nodule	Unknown
5	Strong[8]	1914	30	0	?	Irrelevant	Small	Normal	Pyosalpinx tuberculosa	Pars ampullaris. Platelet, 1 mm. in longest diameter	Tuberculosis
6	Lehmacher[9]	1916	47	Virgin	Regular, scant	Appendectomy at 41 years	Huge myoma	Right: fibroma Left: serous cyst	Elongated to 23 cm., salpingitis isthmica nodosa	Pars isthmica on both sides. Pea-sized nodules	Unknown
7	Lehmacher[9]	1916	56	?	?	Chronic cardiac disease	Normal	Senile atrophy	Chronic salpingitis	Pars ampullaris of left tube	Unknown
8	Reichelt[10]	1928	47	Virgin	?	?	Huge myoma	Normal	Elongated to 10 cm., salpingitis tuberculosa	Pars ampullaris of right tube. Nodule 1.5 cm. in diameter	Tuberculosis
9	Reichelt[10]	1928	85	?	?	?	Senile	Senile atrophy	Pyosalpinx	Pars ampullaris of both tubes. Nodules 3 cm. in diameter	Tuberculosis ?
10	Bârcă[11]	1932	47	0	Menarche at 17	Pulmonary and peritoneal tuberculosis	Normal	Serous cyst of left ovary	Salpingitis tuberculosa	Left tube pea-sized nodule	Tuberculosis
11	Foged[12]	1941	28	0	Menarche at 13	Osteomyelitis at 2 years	Normal	Serous cysts in both ovaries	Salpingitis nodosa?	Several pea- to almond-sized nodules in both tubes	Unknown

My interest in this subject was stimulated by a case operated upon by me in 1927 in the Vienna Lying-in Hospital. As it has not been reported elsewhere I desire to incorporate here some of the photomicrographs from the specimen, because of the highly instructive pictures obtained. The essential features of this case are as follows:

CASE 1.—A 31-year-old nullipara with chronic tuberculosis of the lungs was operated for a pseudointraligamentary cyst of the left ovary, measuring 10 by 8 by 8 cm. The thickened left tube was closely attached to the wall of the cyst and elongated to 13 cm. In its isthmic portion was a hard nodule 7 mm. in diameter and a similar one, measuring 9 mm. was found in the pars ampullaris. The uterus was normal. On the right was a small hydrosalpinx and a cystic ovary.

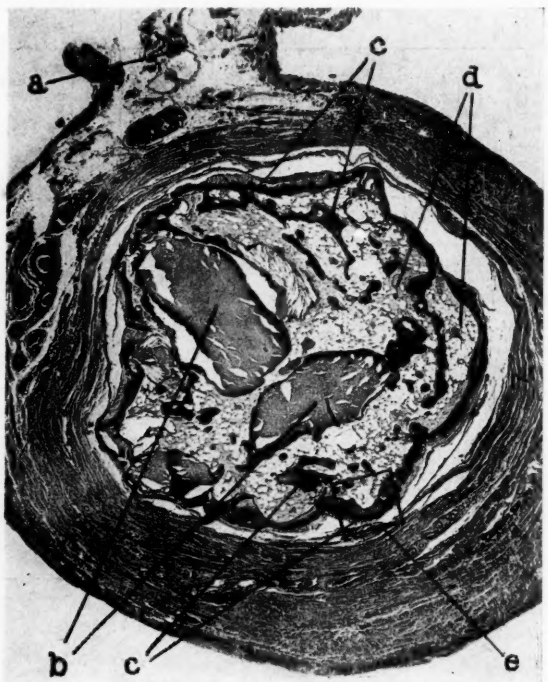

Fig. 1.—Case 1. Pars ampullaris. *a*, Mesosalpinx; *b*, detritus and calcium deposits; *c*, bone trabeculae; *d*, bone marrow; *e*, area of "Fig. 2."

The histologic examination of the left tube shows a most unusual picture (Figs. 1 and 2).

The wall of the pars ampullaris was considerably thickened, the mucosa missing, and the lumen filled by partly calcified bone tissue. The bone trabeculae were arranged irregularly around masses of calcium deposits and detritus. Here and there the trabeculae showed osteoid linings with a few osteoblasts. No signs of osteoclastic resorption could be found anywhere. In between the trabeculae lay bone marrow of which only a small portion looked like typical fat marrow. In most places it was fibrous or of an atrophic, gelatinous character. In the midst of the detritus and also at some places within the bone marrow were

isolated amorphous calcified masses. There was also calcification in the surrounding connective tissue. Numerous empty spaces surrounded by foreign body giant cells suggested by their shape that they contained lipoid crystals. In the pars isthmica the wall was thickened, the folds were scant, and the mucosa was atrophic. The epithelial lining was fairly well preserved but of more cubic character, only a few remaining folds showed cylindrical epithelium. The lumen was filled with detritus and with numerous cells having round or irregularly shaped nuclei. In one area where a bone hard nodule had fallen out on cutting, many bone trabeculae could be seen; the picture in every respect was identical with the one described above.

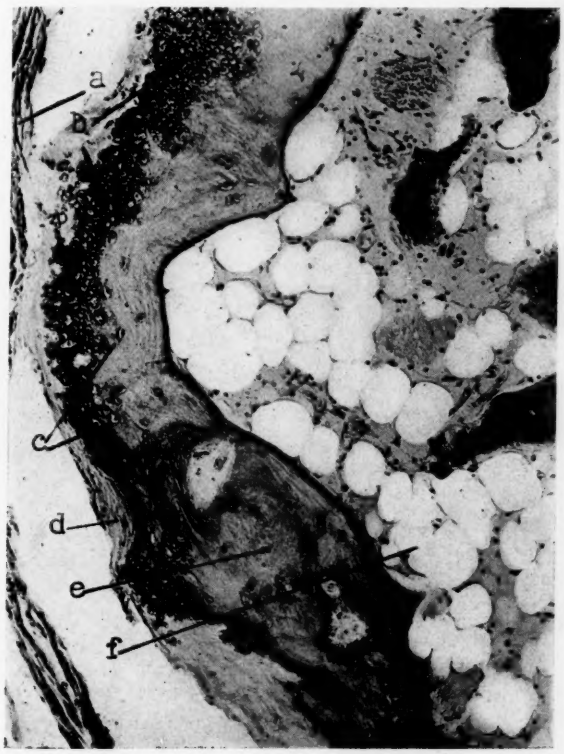

Fig. 2.—Case 1. Area "e" from Fig. 1. *a*, Tube wall; *b*, layer of ossification; *c*, bone corpuscles; *d*, osteoid lining; *e*, bone tissue; *f*, bone marrow.

These histologic findings suggest a chronic indurating salpingitis with local pyosalpinx formation, leading to stenosis and finally atresia of the lumen. In two encapsulated areas, bone formation had taken place. The atrophic, gelatinous bone marrow, the rarity of osteoblastic linings, and the absence of osteoclastic resorption favored the conclusion that the ossification process had come to a standstill. The fact that one could see uncalcified portions in some trabeculae, while on the other hand calcification had occurred not only in conglomerations of old pus but also in the connective tissue protruding into them, in the bony layers surrounding them, and in the hyalinized areas of the eccentric and atrophic tubal wall, makes it probable that we were dealing with two different

kinds of calcification which occurred at different times: A primary one in the detritus of the inflammatory process and a secondary one in the reactively formed bone tissue.

As the patient had a tuberculous pulmonary process, a tuberculous etiology of the inflammation had to be considered. There, however, is no evidence for such an origin in the histologic picture.

CASE 2.*—(Beth Israel Hospital, New York City.) F. G. (Admission No. 32488), a 27-year-old Russian-Jewish, married woman, came to the hospital because of pain in the lower abdomen of several years'

Fig. 3.—Case 2. Pars isthmica. *a*, Tubal folds in pseudofollicular arrangement; *b*, mineral deposits; *c*, osteoid lining; *d*, Haversian system; *e*, bone marrow cavities; *f*, connective tissue of tubal fold; *g*, tubal epithelium; *h*, area of "Fig. 4."

duration, very severe for the past two months. Menstruation had begun at the age of 12 and was always irregular, every thirty-three to thirty-five days, lasting three days; in the past five years only for one to two days, always very scant and painful.

Both parents had tuberculosis. Patient maintained that she had never been ill. She had been married for eight years without ever becoming pregnant.

Medical examination on admission showed nothing unusual.

Gynecologic Examination.—Uterus of normal size, anteverted; to the right a cystic adnexal mass, the size of a man's fist. To the left there was a thickened tube and a somewhat enlarged cystic ovary.

*I am indebted to Dr. H. Lorber for permission to use the clinical data of this case.

Laparotomy (Dr. H. Lorber) showed a right parovarian cyst, 4 inches in diameter. The cyst was unilocular and filled with clear serous fluid. The right tube was flattened against the wall of the cyst, and its fimbriated end adherent to the posterior surface of the normal, anteverted uterus. The left tube showed in its middle portion a nodule the size of a cherry. The pars ampullaris was bulbous, closed, and adherent to the lateral pelvic wall and the ovary. The latter contained a cyst the size of a walnut. The retrocecal appendix had a reddened and bulbous tip.

The parovarian cyst, the right tube, the part of the left tube which contained the nodule, the cyst from the left ovary, and the appendix were removed.

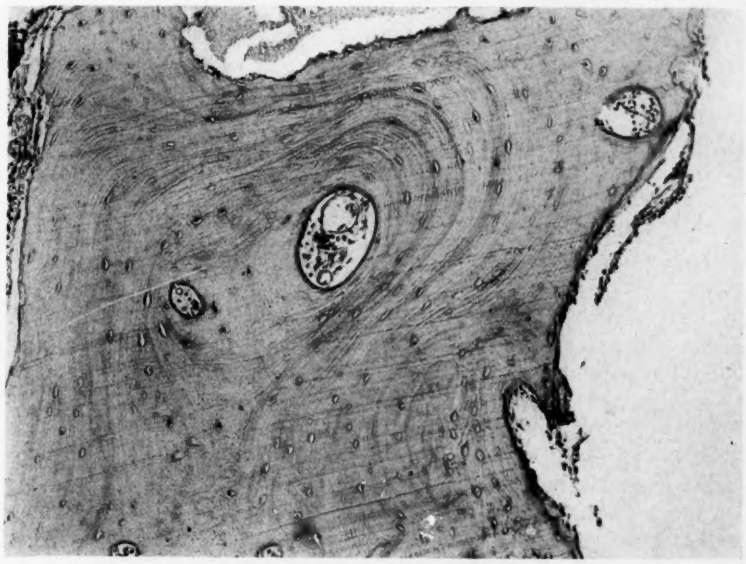

Fig. 4.—Case 2. Area "*h*" from Fig. 3. Lamellar arrangement of bone tissue around Haversian canal.

Examination showed a papillary, right, parovarian cyst, an elongated otherwise normal right tube, a lutein cyst of the left ovary, and a histologically normal appendix. The removed piece of the left tube was 4 cm. long and contained, in the isthmic part, the nodule described above. While trimming the material we encountered small, hard, yellowish particles near the center of the tube. The specimens had to be decalcified for cutting.

Microscopically one sees that only a few tubal folds have remained, which being fused, present the structure of so-called pseudofollicular salpingitis (Fig. 3). Within the connective tissue of the tubal wall appeared an irregular cavity about 3 mm. in diameter. This cavity communicated in places with the remnants of the original tube lumen, in other places it was separated from it only by the epithelium which appeared lifted off or by epithelium plus a few layers of connective tissue cells. This lumen was filled with granular masses which were surrounded

by bone tissue. Numerous leucocytes and cast-off cells with small, dark, shrunken nuclei, and the fibrin surrounding them were evidence of an inflammatory process. In some places where the connective tissue bordered on detritus, it formed a narrow, homogeneous, pale-staining band without nuclei. An identical band formed the outer border of the bony structure in many places, and in Azan-stained slides one could ascertain the identity of these structures. The deeper layers of the bone showed the characteristic lamellar arrangement with Haversian canals and cavities that contained fatty bone marrow (Fig. 4). Since there were no osteoblasts or osteoclasts, the process of ossification must have ended long ago.

CASE 3.*—(Beth Israel Hospital, New York City.) R. F. (Admission No. 44230), a 30-year-old, Polish-Jewish, married woman, came to the hospital because of sterility, pain in the lower abdomen for four years, and an amenorrhea of three months' duration.

Menarche not remembered; menstruation was always irregular, every three to four months, lasting often only one hour, very scant, with mild cramps. This had been assumed to be due to poor ovarian function, and three months prior to admission five stimulative x-ray treatments had been given. As a menstrual interval of three to four months was nothing unusual in this patient, it is not known whether the recent amenorrhea was in any way due to the radiation.

Family history irrelevant.

Patient had typhoid fever as a child. The abdominal pains which started four years prior to admission were attributed to a chronic appendicitis and after two years' observation an appendectomy was performed. The appendix was retrocecal and bound down by dense adhesions. The uterus was infantile and the adnexa normal. This is of interest as it proves that the condition which we are to describe hereafter had developed within the two years between the two operations.

Medical examination on admission showed considerable obesity, probably on an endocrine basis, and a blood pressure of 148/95. The gynecologic findings were: Nulliparous introitus, considerable mucous discharge, a conical cervix in the axis of the vagina, and the uterus in first degree retroversion, normal sized and freely movable. Right adnexa somewhat enlarged and hard. A small dermoid cyst was suspected and an x-ray film made, which showed a "small calcareous circular nodule in the right pelvis at about the location of the right ovary." A Rubin test suggested that both tubes were closed. An attempt at visualization with lipiodol was unsuccessful because the contrast medium permeated into the vessels.

The laparotomy (Dr. I. C. Rubin) showed an infantile uterus. The adnexa were bound down by dense adhesions. Small nodules could be felt in both tubes close to the uterus. On the right was a small tubo-ovarian mass so covered with adhesions that it was impossible to distinguish the outline of the tube, which seemed to be closed in its entire length. The left tube was similarly buried in adhesions and closed. The left ovary contained a small chocolate cyst. The right adnexa, the left tube, and part of the left ovary were removed.

Histologic Examination.—The right ovary was transformed into a cystic mass, 5 by 4 by 1.8 cm. The tube, which was closely attached to

*I am indebted to Dr. I. C. Rubin for permission to use the clinical data of this case.

the ovary by dense adhesions, measured 5 cm. in length and appeared thin. The fragment of the proximal portion, containing the nodule, had been severed at the time of operation, apparently for inspection, because of its unusually firm consistency. Three centimeters farther distally a similar very hard, small, round resistance could be felt. It could be shifted and when stretching the outer layers of the tube over it, appeared as a yellowish mass. In the pars ampullaris several other such small yellowish masses could be found nearer to the serosal surface. Other irregularly shaped small yellow nodules could be seen on the surface of the ovary.

The specimens from the left ovary and left tube showed nothing unusual microscopically. The right ovary contained many cysts, some luteinic, others lined with layers of granulosa cells, still others only with a single layer of flat cells. The nodules on the surface described above consisted of fibroblasts which partly formed foreign body giant cells. They were grouped around lancet-shaped spaces, which contained highly refractive, colorless, glassy masses. The nodules were surrounded by dense connective tissue.

The right tube was cut partly in serial sections, partly in interrupted serial sections. In the slides from the proximal isthmic part the tubal folds were infiltrated with large mononuclear elements and with a few leucocytes. The epithelium was intact and the outer layers were not inflamed.

In the area of the distal isthmic nodule no lumen surrounded by mucosal folds could be seen. There were only occasional glandlike enclosures, lined with an uncharacteristic flattened epithelium but without communication with each other and surrounded by dense connective tissue. In the midst of this connective tissue there was an irregular space about 2 by 3 mm., filled with pale, red-staining granular detritus. Whether this area corresponded to the former tube lumen or whether it represented a necrotic focus in the tubal wall could not be ascertained. Around this area the connective tissue bundles showed a concentric circular arrangement. Along about one-half of the circumference the bordering connective tissue showed a different character (Fig. 5). Its bundles were coarser, there were fewer nuclei, the intercellular substance becomes wider and homogeneous and finally merges into a red-staining, osteoid anuclear zone. Between this zone and the detritus, a young vascular granulation tissue had grown in, with numerous fibroblasts, which formed a fine meshwork, filled with round cells. One of the serial sections showed an oval giant cell of the Langhans type in the granulation tissue (Fig. 6). The fibroblasts were partly transformed into osteoblasts and formed a shell of true bone tissue around the detritus and small bone trabeculae on the edge of the osteoid tissue. One could see the beginning of lamellar arrangement in the ground substance and the fibroblasts becoming ensheathed by the intercellular substance, taking on the characteristic stellar shape of bone corpuscles. There were very thin layers of bone in some slides, while in others solid lamellar bone structure with perfectly arranged Haversian canals were found. Then the bone became thinner again and disappeared for a few slides completely, only to reappear again in the same manner.*

*I wish to thank Dr. A. Plaut, Beth Israel Hospital, New York City, for permission to use the specimens of Cases 2 and 3 from his collection and for his kind help and advice in the description and interpretation of these rare findings.

CASE 4.*—(Sloane Hospital for Women, New York City.) M. L. (Admission No. 403213), a 37-year-old widowed negress, came to the hospital because of backaches, duration one year, and a growing mass

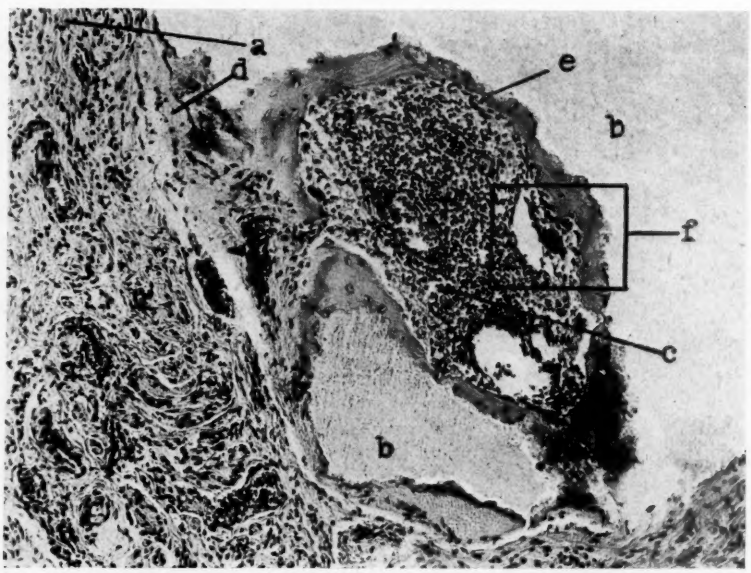

Fig. 5.—Case 3. *a*, Muscular wall; *b*, fibrin and mineral deposits; *c*, granulation tissue; *d*, osteoid tissue; *e*, osteocytes; *f*, area of "Fig. 6."

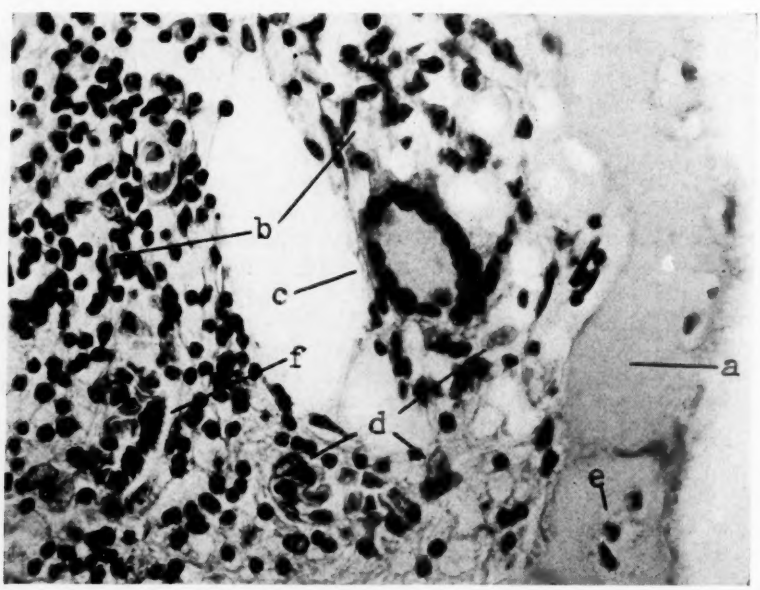

Fig. 6.—Case 3. Area "*f*" from Fig. 5. *a*, Bone tissue; *b*, granulation tissue; *c*, giant cell; *d*, fibroblasts; *e*, bone corpuscles; *f*, capillaries filled with red blood corpuscles.

*I am indebted to Dr. B. P. Watson for permission to use the clinical data of this case.

in the lower abdomen. Menstruation had begun at the age of twelve years and was somewhat irregular, interval about twenty-eight days, duration three days, and always scanty. For the past nine months the amount of flow had been increased.

The patient's husband died from tuberculosis. Family history irrelevant otherwise.

Patient had typhoid fever and malaria at the age of fourteen. In recent years she had repeated attacks of severe tonsillitis. She had bronchopneumonia due to hemolytic streptococci at age of thirty-five.

Medical examination on admission showed old lesions of chorioretinitis of unknown origin in the left eye. Nothing else of importance.

Gynecologic Examination.—Uterus was transformed into a firm irregular mass, reaching two fingers above the umbilicus. Adnexa were not made out. A diagnosis of a large fibroid of the uterus was made.

Fig. 7.—Case 4. Pars ampullaris. *a*, Muscle bundles; *b*, tubal folds in pseudofollicular arrangement; *c*, well-preserved tubal epithelium; *d*, calcium deposits; *e*, bone tissue; *f*, coarse, dark-staining calcium granula with ingrowing connective tissue; *g*, fibroblasts growing along the mineral deposits.

Laparotomy (Dr. H. Halsted) showed multiple adhesions between the ileum, parietal peritoneum, and the genital organs. There was, at the site of attachment of the ileum to the anterior abdominal wall, a cluster of partially caseous calcified material. This mass was left undisturbed. The uterus contained several large fibroids. There was a chronic salpingitis on one side; the condition of the other tube is not described. One ovary contained a small serous cyst, the other a small abscess with

calcification. Supracervical hysterectomy and bilateral salpingo-oophorectomy were performed.

Pathologic examination of uterus and ovaries showed nothing remarkable. One tube, however, showed a most unusual picture: It was 6 cm. long and its fimbriated end had been incorporated with parts of the adjoining ovary into a stony hard mass, 2 cm. long and 0.75 cm. in diameter.

Microscopically, in the proximal part of the pars ampullaris only slight chronic inflammatory changes could be seen. There was an irregular thickening of the muscular coat with evidence of increased connective tissue. There was increased vascularization of the muscle layers, and

Fig. 8.—Case 4. Pars ampullaris. *a*, Young granulation tissue; *b*, bone marrow; *c*, bone trabeculae; *d*, transition from connective tissue into osteoid zone; *e*, calcium deposit with beginning bone formation on the edges; *f*, calcification in a bone trabecle; *g*, beginning lamellar arrangement, osteocytes.

perivascular infiltrates with lymphocytes and plasma cells could be seen. The tubal folds were elongated and thickened. Infiltrates, similar to the ones described above, were noted perivascularly in the stroma of the folds. The tubal epithelium appeared normal.

Farther distally in the pars ampullaris, the normal structure of the tubal wall had been completely destroyed. Only occasionally could one recognize a few strands of circular or longitudinal muscle bundles. Of the tubal folds one could find only remnants, which had become adherent to each other, presenting the picture of a salpingitis pseudofollicularis.

The tubal epithelium was, on some folds, well preserved; in the dilated pseudofollicles it formed a low cuboidal lining. Most of the tubal wall had been replaced by extensive masses of partially hyalinized fibrotic scar tissue. These masses extended everywhere beneath the mucosa, and thus deformed the wall as well as the lumen. They surrounded huge areas of calcium deposits and detritus, in which numerous lymphocytes and plasma cells could still be recognized.

Partly in the midst of these calcified masses and partly bordering them lay a network of true bone tissue in characteristic trabecular arrangement. Different forms of bone formation could be observed.

Where the connective tissue bundles of the tubal wall ran parallel to the borders of the calcium deposits, their inner layers had become hyalinized. There were fewer and fewer nuclei, and finally there was a homogeneous pale red-staining osteoid zone with gradual transition into bone tissue. In other areas, a young vascular granulation tissue penetrated into the calcium deposits, splitting them up into many islands and forming bone trabeculae on their edges. Where the fibroblasts had become ensheathed in the intercellular substance, they took on the characteristic stellar shape of osteocytes. The spaces between the bone trabeculae were filled with a loose connective tissue containing masses of plasma cells, lymphocytes and monocytes in its meshes. In other areas there was real fatty bone marrow but fully developed myelopoetic tissue could not be found.

The masses of calcium deposits and detritus surrounded and interspersed by hyaline connective tissue and bone trabeculae extended into the broad ligament and to the surface of the ovary. Within the hyalinized connective tissue there were spindle-shaped cracks as sometimes found with old tuberculosis. There was, however, nothing that would prove a tuberculous process. All one can say is, that there was evidence of an old chronic salpingo-oophoritis, probably a tuboovarian abscess, extensive necrosis with subsequent calcification and finally intensive reaction of the surrounding connective tissue with the formation of true bone structure.

COMMENT

A completely satisfactory explanation for all pictures encountered is as yet lacking. Cartilage has never been found in any of these cases. There was also never any evidence of relationship to embryonic inclusions or dermoids. One could also think of remnants of an old ectopic pregnancy, but nothing in the case histories, the clinical or histologic findings, supports such an assumption. Older theories like "osteoblast-metastasis" (Klebs) or "embolisms of bone marrow-giant cells" (Jerusalem) may be mentioned as Maximow has proved that such cases do occur. Virchow considered such bone formations to be the end products of a chronic inflammatory process and this theory has been generally accepted since. So far as one can judge from the histologic pictures in the four cases presented in this paper, the bone tissue seems to have formed in three different ways: Where the connective tissue of the tubal wall runs parallel to the bone lamellae, the process resembles periosteal bone formation. In other places one can follow the connective tissue bundles into the periosteal tissue and finally into bone.

Here we have a direct metaplasia according to Maximow, analogous to intermembranous bone formation. Finally we have the osseous bars formed around and in the midst of the calcium deposits by osteoblast, which arise from the fibroblasts of the young granulation tissue. These young cells have much the same properties as the primitive reticular cells of the blood-forming tissues (Maximow). The granulation tissue dissolves and resorbs the mineral deposits and penetrates into the slits thus formed. These cavities become the new bone marrow cavities, and from here the osteoblasts form the bone tissue on the remnants of the detritus and calcified connective tissue.

Further understanding of the processes involved might be gained from animal experiments. Sacerdotti and Frattin[13] were the first who succeeded in obtaining heteroplastic bone formation in tissues which normally have no osteogenic properties. Using the kidneys of rabbits for their experiments they tied the pedicle, leaving only the very limited blood supply from the cortex. After several weeks calcium deposits appeared in the connective tissue beneath the pelvis and after three months a lining of bone tissue formed around the calcified areas. In a few cases a homogeneous osteoid tissue was noted, exactly like that seen in some of our slides. Poscharissky, working with kidneys, obtained the same results. With the liver, spleen, or ovaries, however, complete atrophy without bone formation occurred. This difference in the outcome is due to the blood supply, which the kidney tissue retains from the capsule. These vessels maintain sufficient circulation to prevent necrosis. They also furnish the capillaries for the granulation tissue, which grows into the calcified foci of the kidney medulla. The calcified tissue plays the role of the primordial cartilage. Poscharissky believes that organic substances, remnants of exudate between the calcium salts, furnish the stimulus for the transformation of the fibroblasts into macrophages, which destroy and resorb the calcified tissue, and into osteoblasts which form the new bone tissue. In the bone formations in the lungs one can see coal particles within the osteoblasts, which proves their origin from connective tissue cells.

From these experiments it would seem that an almost complete interruption of circulation is a necessary forerunner of such bone formations. In the tubes, with their excellent blood supply, such an occurrence must of necessity be extremely rare. Extreme elongation and compression by tumors of the uterus or the ovaries and kinking and constriction by dense adhesions were present in at least 10 of the 15 cases. Whether this and the pressure of the detritus masses against the distended tubal walls could have created such a condition of almost, but not quite complete, interruption of circulation as in the animal experiments, we do not know. The fact remains that in thousands of similar cases no bone formation occurred.

In three cases a diagnosis of tuberculosis was made, in three others a tuberculous origin was assumed. One must not forget, however, that,

for many years giant cells of the Langhans type were erroneously considered absolute proof of tuberculosis. So far as calcium deposits are so frequent in tuberculous inflammations, one could understand some causal relation to ossification, but the frequency of genital tuberculosis and the rarity of bone formation forces us again to assume other coexisting causative conditions. Of what nature these may be we can only guess. Most authors describe the bone formation as a metaplastic process, but we have learned that many pictures which used to be called metaplasia have to be really considered primary tissue malformations. This is particularly true in the female genital tract (R. Meyer). Fischer-Wasels[14] likewise warns against the assumption of a normal potency of the connective tissue to metaplastic bone formation. He maintains that an "inborn disposition," perhaps of endocrine or chemical nature, must be present. In this connection it is interesting to note that so far as one can judge from the case reports, 12 out of the total of 15 patients had an endocrine disturbance (4 certain, 8 probable). It might well be that a combination of the three: tissue malformation plus abnormal chemism plus chronic inflammation or circulatory damage must occur to produce these unusual anatomic changes. Such an assumption of multiple determination would at least explain the rarity of their occurrence.

So far as the nomenclature is concerned, the name "osteoma tubae" used by Emelijanow and also Dietrich[15] in Halban-Seitz's *Handbuch* is a misnomer. As the latter author says very rightly, osteoma means a bony tumor, whereas these formations have no neoplastic character. To speak of metaplastic or heteroplastic bone formation is not justified as both expressions would pretend a knowledge of the histogenesis in these cases which actually we do not possess. These names given by Virchow, backed by his authority and accepted by all authors since, have caused us to be satisfied with an explanation for the bone formation, i.e., metaplasia on an inflammatory basis, which is inadequate. As long, therefore, as the etiology is not clear it is preferable to avoid a definite nomenclature which only tends to obscure the fact that the problem is as yet unsolved.

The condition reported here is, of course, mostly of theoretic interest. The only practical point was brought out by Bârcă and recently by Foged, who found shadows in their x-rays which corresponded to the bone formations. Also in Case 3, as mentioned above, such a shadow was found. It is, therefore, necessary to include the rare possibility of "bone formation in the tube" in the long list of possible interpretations of x-ray shadows in the female pelvis.

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TRANSPLANTATION OF FASCIA FOR RELIEF OF URINARY STRESS INCONTINENCE*

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WITHIN less than one hundred years, gynecologists have developed and perfected surgical techniques which can be relied upon to relieve most of the symptoms which are the result of birth injuries to the female sex organs. Factors which contribute to poor results or failures in vaginal plastic surgery include those that arise from:

1. Congenital underdevelopment of the injured structures.
2. Extensive loss of tissue substance resulting from the primary injury or from post-partum infection and tissue necrosis.
3. Increased tissue damage resulting from lack of judgment and skill in applying accepted gynecologic surgical techniques.

Efforts to repair a birth injury are not infrequently handicapped by the results of one or more previous unsuccessful attempts to cure the same condition.

One of the most difficult symptoms to relieve by vaginal plastic surgery is urinary stress incontinence. Statistics prove that 10 to 20 per cent of operations for conditions causing this symptom either fail or are only partially successful. It is with the group of cases in which one or more vaginal plastic operations have failed to cure urinary incontinence that this report is particularly concerned.

Unfortunately, we have not yet acquired either a complete knowledge of the anatomic structures in and about the female urethra or an entirely satisfactory explanation of the physiology of the delicate urethral sphincter mechanism which is responsible for the control of urination.

*Read at a meeting of the New York Obstetrical Society, March 10, 1942.

Vaginal plastic operations to restore urinary continence invariably include two fundamental objectives:

1. To reduce the caliber of the overstretched lumen of the urethra to what is recognized as normal, including repair of the torn sphincter muscles.
2. To replace the urethra to its normal position beneath the pubic arch and to reconstruct a proper support from the surrounding tissues.

In some patients, in whom both of these objectives appear to have been accomplished, urinary incontinence is not entirely relieved. Some of the failures follow expert vaginal plastic procedures and satisfactory wound healing.

The importance of urinary tract infections as a factor in the etiology of urinary incontinence is well recognized. Elimination of inflammatory lesions of the bladder will stop leakage of urine in some cases in which it seems that vaginal plastic operations have failed. A routine preoperative investigation of the urinary tract before attempting to relieve urinary incontinence by surgical means might lead to a reduction in unsatisfactory results.

In some instances, the partial successes or failures are probably not due so much to faulty techniques as to the fact that there has been unusual destruction of the urethral sphincter muscles themselves and perhaps of their nerve and blood supply.

In the causation of urinary stress incontinence, the importance of birth injuries to the nervous mechanism which controls bladder function, probably has not received the attention it deserves. In their efforts to cure urinary stress incontinence by vaginal plastic surgery, operators have been accustomed to proceed on the assumption that it is essentially the result of trauma, over-stretching, and permanent relaxation of the urethral sphincter muscles themselves.

Our knowledge of the nerve supply to the bladder and urethra is fairly complete. However, except in cases in which urinary symptoms are caused by spinal cord lesions, we do not yet have the means to be certain that partial loss of urinary control is neurogenic in origin. In other words, we do not have diagnostic methods to determine the extent to which injuries to intrinsic nerves or to nerve endings supplying the urethral sphincter muscles may be responsible for urinary incontinence in any case under investigation. This is unfortunate as there is reason to believe that unrecognized nerve injuries may account for some of our surgical failures. In such circumstances or when the sphincter muscles have undergone too much destruction, complete restoration of function by the usual vaginal plastic procedures can hardly be expected.

With this in mind, various attempts have been made to utilize adjacent anatomic structures with the purpose of providing proper support for the urethra and of developing a substitute muscular sphincterlike action to replace the one that has been lost through birth injury.

Since 1900, numerous surgical techniques have been described in which transplantation of one of seven different muscles or the round ligaments has been recommended to relieve urinary incontinence. This presentation would hardly be complete without brief comments regarding some of these procedures.

In 1910, Goebell[1] reported on the transplantation of the pyramidalis muscles. In his technique, the muscles were freed except at their attachment to the pubic crest. The free ends were passed backward above the pubic bone and sutured beneath the urethra at its junction with the bladder.

In 1914, Frangenheim[2] modified the Goebell technique by leaving the freed pyramidalis muscles attached to strips of the overlying fascia. These combined strips of muscle and fascia were then placed about the urethra by the same route as described in the original Goebell procedure. Frangenheim also recommended that strips of the rectus abdominis muscles be used when the pyramidalis muscles were found to be poorly developed.

In 1917, Stoeckel[3] recommended that the Goebell-Frangenheim procedure be combined with a vaginal plastic operation with plication of the muscular structures about the vesical neck. This procedure is now referred to as the Stoeckel or Goebell-Frangenheim-Stoeckel technique for urinary incontinence.

In 1907, Giordano[4] described a technique whereby enough of the distal end of the gracilis muscle was dissected free from the inner surface of the thigh to allow it to be transplanted to where it could be wrapped about the urethra and sutured in that position. In 1926, Deming[5] reported an excellent result by use of this method in a case of epispadias.

In 1911, Squier[6] recommended the use of the levator ani muscles. Various methods of using these muscles have been devised. One is to free strips of the mesial margins of these muscles and to suture them together between the urethra and vagina. Another is to detach partially a portion of the mesial border of one of the levator muscles and to transplant it between the urethra and vagina. Attempts have also been made to suture the mesial margins of the levator muscles together in the midline between the urethra and vagina without any detachment of their fibers.

In 1923, Thompson[7] transplanted strips of rectus muscle and fascia downward in front of the pubic bone and sutured them around the urethra and vulva. In 1932, Miller[8] recommended that strips of fascia and the pyramidalis muscles be used in a manner similar to that described by Thompson.

In 1929, Martius[9] described a procedure by which he mobilized the bulbocavernosus muscle and some of its surrounding fatty tissue. This muscle-fat pad was then transplanted between the urethral and vaginal walls.

The purpose in all of these techniques was to prevent the escape of urine by providing external pressure on the urethra as a substitute for the normal sphincter mechanism which had been destroyed or was congenitally absent. Transplantation of muscle is an important feature of every technique with the hope that its contractility will be retained and

sphincterlike action will be developed. From a careful study of all these procedures, it seems unlikely that the pyramidalis, strips of levator or recti muscles, the gracilis or bulbocavernosus muscles can be mobilized and displaced to the positions recommended without almost complete destruction of their nerve and blood supply. In addition to this, there is always uncertainty as to the development of the pyramidalis and bulbocavernosus muscles.

Through experience it has been found that in some cases of stress incontinence of urine, the production of a urethral stricture is sufficient to effect a cure. It seems fairly certain that the good results claimed for all the techniques briefly described above have been attained through improved support for the urethra and partial urethral strictures.

In 1933, Price[10] reported on a technique he used to relieve urinary incontinence in a young woman who had congenital absence of the coccyx and sacrum. Loss of urine was neurogenic and congenital in origin. The procedure that he worked out is of interest, because it incorporates the fundamental principle which has been employed in the new technique that I wish to present. In the technique he used, a strip of fascia lata was passed beneath the urethra by the suprapubic route and the free ends were fixed to the recti muscles 5 cm. above the pubic bone. He had great difficulty in passing the fascia beneath the urethra. Although he accidentally opened the bladder and the wound subsequently became infected, the patient was eventually cured of her urinary incontinence.

PROCEDURE

Fig. 1 (*a* and *b*) represents diagrammatically a new surgical procedure for the cure of female stress incontinence of urine. It is like the Stoeckel technique in that it utilizes strips of fascia from the aponeurosis of the oblique muscles of the abdomen which are displaced backward above the pubic bone and sutured beneath the urethra to form a supporting sling. Success of the Stoeckel technique is supposed to depend upon leaving the fascial strips attached to the pyramidalis muscles with the hope that by their contraction the urethra will be compressed thereby preventing the escape of urine from the bladder.

The technique to be described differs from the Stoeckel procedure in that the aponeurotic strips *A* are passed through instead of between the recti muscles *R* at about 4 cm. above the pubic bone *P* (Fig. 1, *a*), before they are sutured to form a sling beneath the urethra *U*. When the abdominal wall is relaxed, it settles backward toward the abdominal cavity. Upon straining, as with lifting, sneezing or coughing, it bulges forward. This has the effect of changing the location of the relaxed recti muscles (Fig. 1, *b*, R^1) to a position represented by the dotted line (Fig. 1, *b*, R^2). This automatically results in a compression of the urethra *U* through the pull of the recti muscles on the fascial sling *A*.

Success of this technique in curing urinary incontinence can probably be increased if it is combined with the usual vaginal plastic steps which are ordinarily employed to:

1. Reduce the caliber of a relaxed urethra to its normal size, including repair of its torn sphincter muscles.

2. Restore a displaced urethra to its normal position beneath the pubic arch.

Figs. 2 to 10, inclusive, show the consecutive steps of the new technique which was successfully used to cure urinary incontinence in a woman in whom two previous vaginal plastic operations had failed.

Fig. 2 shows the midline of the anterior vaginal wall being placed under tension with Allis clamps from the external urinary meatus to a point about halfway to the cervix. The dotted line indicates the line of the original incision used to expose the muscular walls of the urethra *U* and bladder *B*, as shown in Fig. 3.

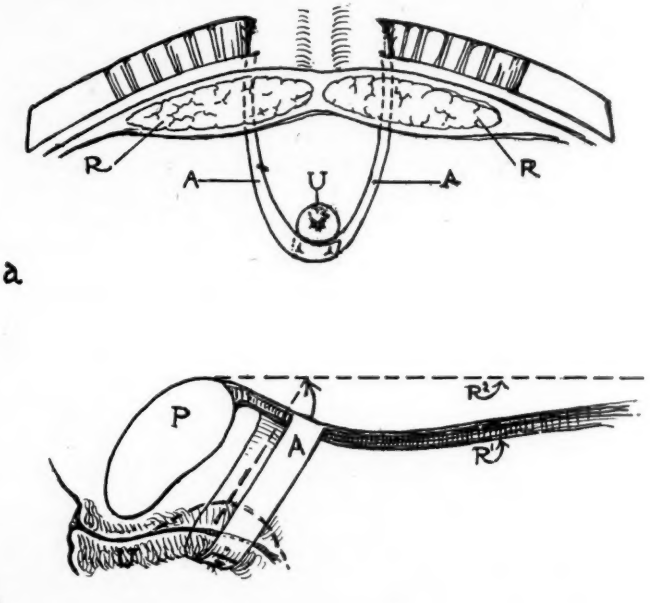

Fig. 1.—*a*, Diagrammatic representation of a technique of transplanting strips of rectus abdominis fascia for cure of urinary incontinence. *A*, Strips of rectus abdominis fascia; *U*, urethra; *R*, recti muscles. *b*, *U*, Urethra; *P*, pubic bone; *A*, rectus abdominis fascial sling; R^1, relaxed position of recti muscles; R^2, position of recti muscles when contracted as with straining.

This incision is carried through the vaginal mucous membrane, the entire thickness of the muscular wall of the vagina including a layer of connective tissue, Fig. 3, E^1, which can be seen as a smooth glistening layer intimately attached to its outer bladder surface. If the incision is carried to this plane of cleavage and the bladder is displaced, it will be noted that on either side of the midline there is another dense layer of connective tissue, Fig. 3, E^2, which is attached to the musculature of the bladder wall, Fig. 3, *B*.

There is still difference of opinion as to the origin of the layers of connective tissue E^1 and E^2, but they are probably no more than hypertrophied layers of the connective tissue which act as supporting structures for the muscle fibers of the vaginal and bladder walls. Between the vaginal and bladder walls and extending between the connective tissue layers E^1 and E^2, there is another thin layer of loose areolar tissue which is a part of the endopelvic fascia. It is in this layer of loose areolar

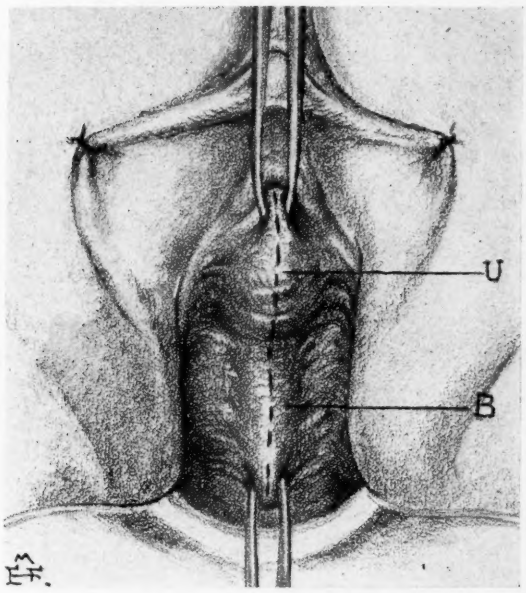

Fig. 2.—Dotted line shows location of original incision in anterior vaginal wall. *U*, Urethra; *B*, bladder.

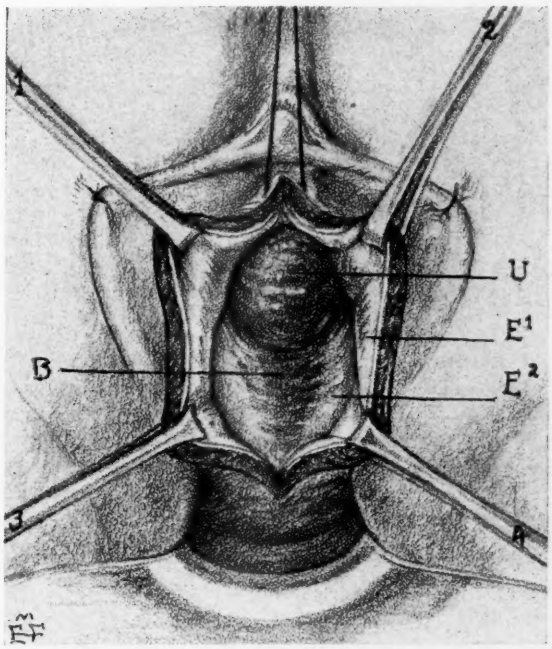

Fig. 3.—Anterior vaginal wall opened exposing the muscular walls of the urethra and bladder. *U*, Urethra; *B*, bladder; E^1, connective tissue layer on outer bladder surface of vaginal wall; E^2, connective tissue layer on bladder wall.

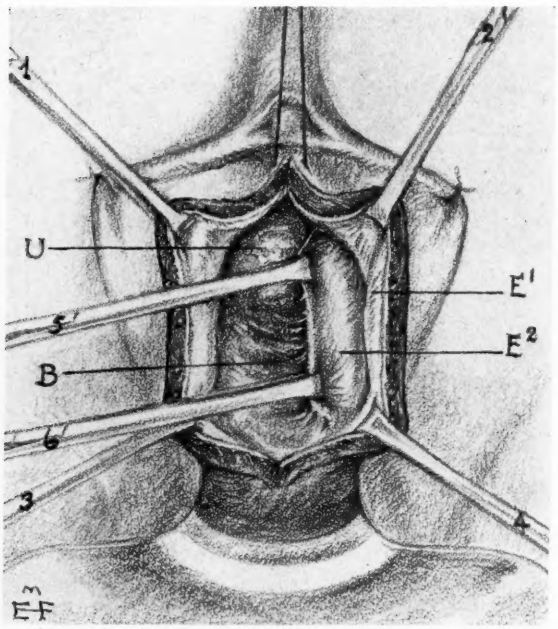

Fig. 4.—Connective tissue layers E^1 on the vaginal wall and E^2 on the bladder wall being held under tension by use of Allis clamps, *2* and *4*, and *5* and *6*.

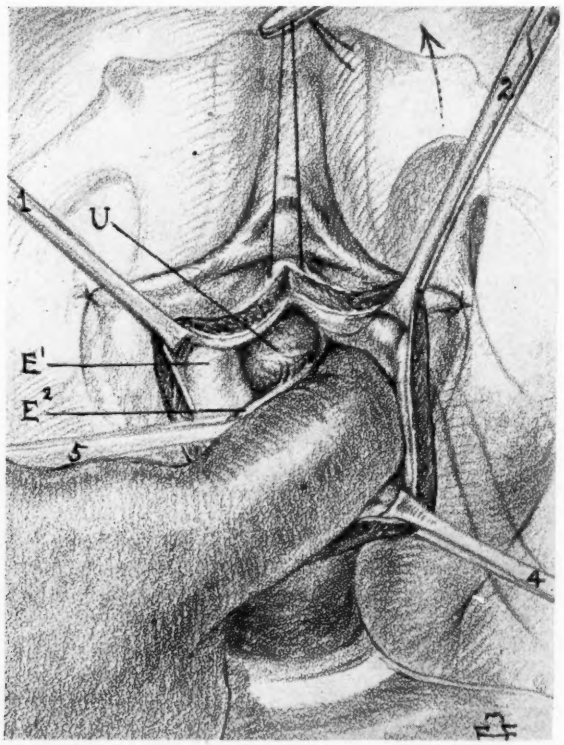

Fig. 5.—By blunt dissection the plane of cleavage between E^1 and E^2, shown in Fig. 4, has been opened laterally and forward. The finger is being passed through this opening forward and above the pubic bone at the left of the urethra *U*.

tissue that practically bloodless blunt dissection can be carried out in every direction. In fact, there is no other natural plane of cleavage in the anterior vaginal wall. Attempts at dissection in any other plane may result in hemorrhage which is troublesome and difficult to control.

By keeping the layers of connective tissue E^1 and E^2 on the bladder and outer surface of the vaginal wall under tension with Allis clamps, *1* and *2* and *5* and *6*, as shown in Fig. 4, it is possible by blunt dissection to open an almost bloodless space between E^1 and E^2 which can be extended forward on either side of the urethra.

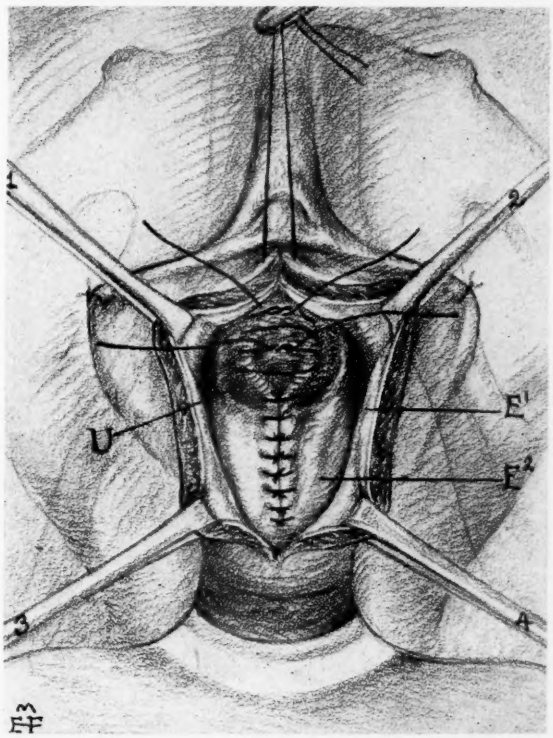

Fig. 6.—The wall of the urethra *U* is being infolded with mattress sutures to reduce its caliber and to reunite the torn ends of the sphincter muscles. The mesial margins of the connective tissue layer E^2 on the bladder have been brought into apposition with chromic catgut sutures.

Starting in this plane of cleavage, it is easily possible, as shown in Fig. 5, to pass a finger upward behind and above the pubic bone nearly to the point of attachment of the abdominal muscles to the pubic crest without risk of injury to the bladder or urethra and with very little bleeding.

Fig. 6 shows the lumen of the overstretched urethra being reduced in size by mattress sutures of fine chromic catgut which infold its wall and bring into apposition the torn ends of the urethral sphincter muscles.

Figs. 6 and 7 also show how the thinned-out mesial margins of the connective tissue E^2 on the bladder wall are united in the midline by interrupted sutures of fine chromic catgut to provide additional support for the bladder and urethra.

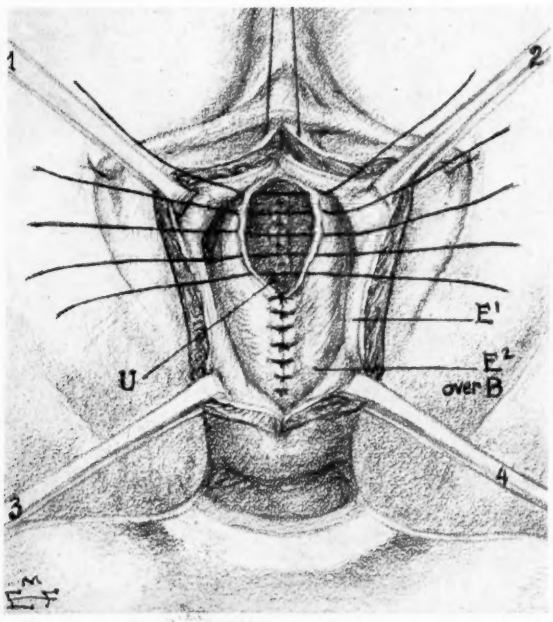

Fig. 7.—Apposition of the mesial margins of the connective tissue layers E^2 is being carried forward over the urethra for additional support.

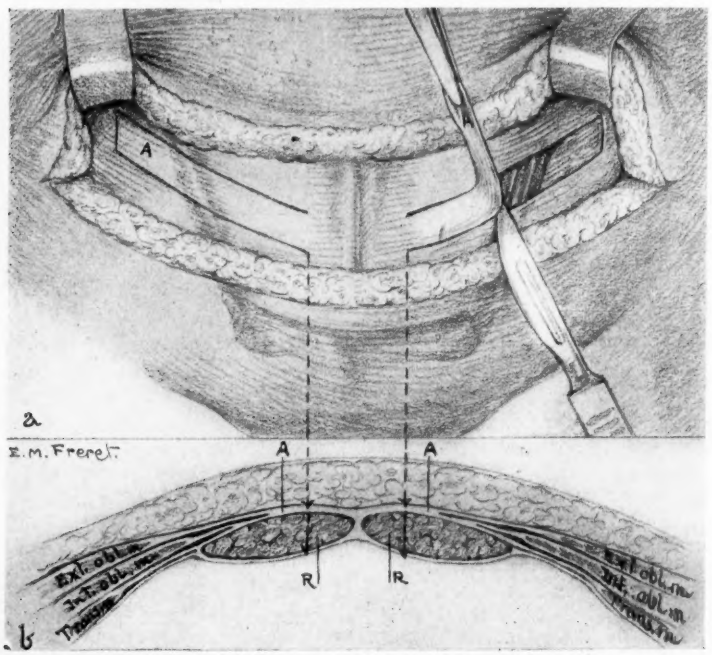

Fig. 8.—*a*, Fascial strips *A* from the aponeurosis of the oblique muscles are being separated through a Pfannenstiel incision. *b*, The dotted lines indicate points about 2 cm. from the mesial margins of the recti muscles *R* through which the fascial strips *A* are passed backward before encircling the urethra.

Having completed these steps in the vaginal part of the procedure, the aponeurosis of the oblique muscles of the abdomen is exposed through a Pfannenstiel incision as shown in Fig. 8, *a*.

A strip of the aponeurosis *A*, about 6 cm. in length and 1.5 cm. in width is then dissected free, starting at the outer end on either side and carrying the dissection to within about 2 cm. of the midline where it is

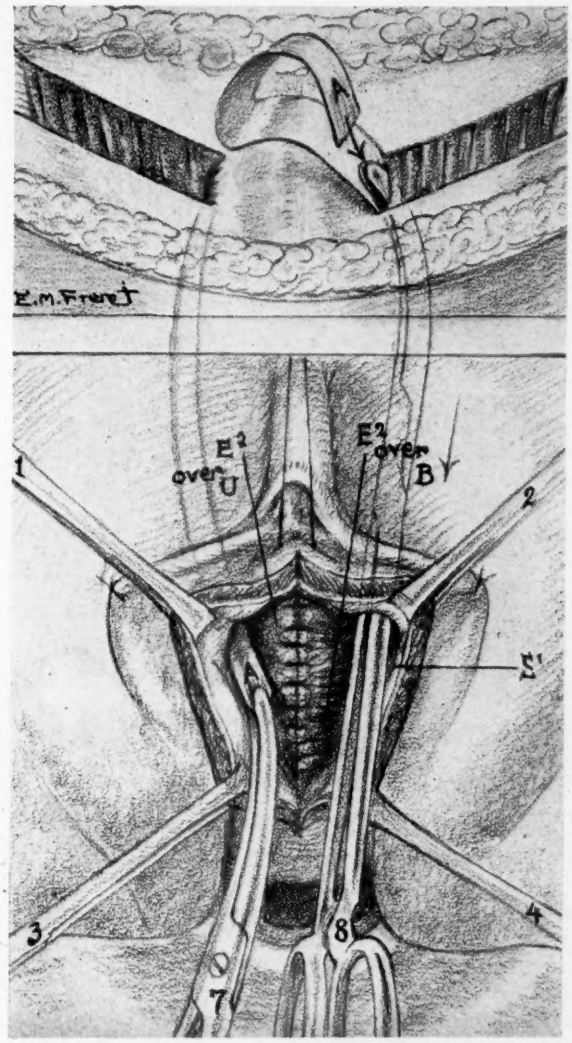

Fig. 9.—Clamps 7 and 8 passed forward in the spaces opened by finger dissection as shown in Fig. 5 are being used to grasp the fascial strips *A* and to draw them into the vaginal wound with one on either side of the urethra.

left attached. The arrows on the dotted lines projected from the attached ends of the aponeurotic strips *A*, to the cross section of the abdominal wall in Fig. 8, *b*, indicate points about 2 cm. from the inner margins of the recti muscles *R*, through which the strips are passed as they are drawn backward along either side of the urethra.

Fig. 9 shows how clamps *7* and *8* are passed forward above the pubic bone through spaces opened by finger dissection as shown in Fig. 5. Clamp *8* has been forced gently forward through between the fibers of the rectus muscle and is about to pick up the tip of the aponeurotic strip *A*. By use of clamp *7*, the fascial strip has been drawn backward into the vaginal wound. After the fascial strips have been brought into the vaginal wound on either side, they are placed under the urethra as shown in Fig. 10, and are sutured together with sufficient tension to slightly elevate the urethra at about the point at which it connects with the bladder.

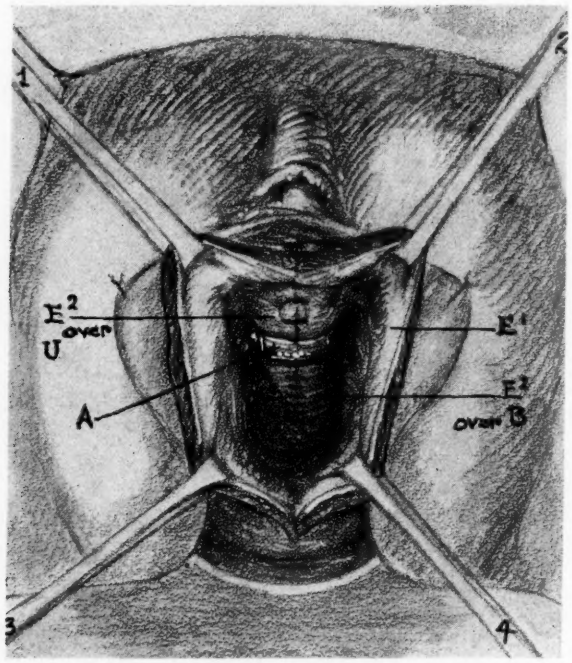

Fig. 10.—The fascial strips *A* have been united in the midline to form a fascial sling beneath the urethra at its junction with the bladder.

When this has been accomplished any excess tissue is excised from the anterior vaginal wall and the incised margins of the wall are brought into apposition in the midline with interrupted chromic catgut sutures. The abdominal incision is carefully closed in layers to prevent the development of an incisional hernia. Sulfanilamide powder is placed in the abdominal wound, as it is obvious that with this technique there is some risk that infection may be carried into the wound from the vagina.

In the technique as described, aponeurotic fascial strips were developed through a low transverse abdominal incision. If preferred, longitudinal rectus abdominis fascial strips, obtained in the same manner through a low midline incision, may be used. When the opportunity presents itself, it is proposed to try the use of a strip of the fascia lata of the thigh. If this was done, it would seem wise to draw the ends of the strip forward through the vaginal wound and between the fibers of the recti muscles. They could then be united between the recti muscles and

its overlying fascia, leaving a loop of fascia as a sling beneath the urethra. Theoretical advantages of using a strip of fascia lata are:

1. It would avoid difficulties encountered in getting fascial strips in patients who have scars of previous abdominal incisions.
2. By avoiding the necessity of excising any abdominal fascia and eliminating the necessity for a rather long abdominal incision, the chances of wound infection and postoperative incisional hernia might be reduced.
3. By use of a fascia stripper, an adequate strip of fascia lata could be obtained through two small skin incisions of the thigh.

COMMENT

The new procedure that has been described was devised primarily with the hope of curing post-partum, urinary stress incontinence in women in whom vaginal plastic surgery seemed inadequate. As pointed out, surgical failures by the vaginal route may be due either to excessive damage to the urethral sphincter muscles or possibly to unrecognized injuries to the nervous mechanism which controls the functions of the urethra and bladder. If, by further experience, it can be shown that it is reasonably successful in such cases, it is hoped that the same technique can be used to develop urinary continence in women in whom it is necessary by plastic surgery to construct a urethra. This includes women in whom the urethra is partially or completely absent as a result of congenital malformations or destruction from birth injuries.

The disadvantages of the procedure are that it requires a painstaking technique which should not be undertaken by a surgeon who has not acquired a modern conception of the anatomic structures in the anterior vaginal wall about the urethra and bladder. Dissection in this region is safe and nearly bloodless if carried out in the planes of cleavage described above. If these tissue planes are not followed, blood loss may be excessive and the bladder and urethra may be subjected to serious damage. Difficulties in the dissection are increased by the fact that this technique is particularly suited to patients who have had one or more previous unsuccessful vaginal plastic operations for the same condition. In such circumstances, considerable scar formation is likely to be encountered.

It seems fair to state that the new procedure which has been described has certain advantages over those previously recommended, in that:

1. It utilizes the rectus abdominis muscles which are always well developed and easily accessible.
2. It involves no displacement of the recti muscles or possible loss of function through damage to their nerve or blood supply.
3. It develops a fascial sling in a position and manner which provides additional support and external pressure to the urethra at the point where it is likely to be most effective, i.e., at the junction of the urethra and bladder.

4. It takes advantage of the favorable anatomic relationship of the recti muscles to the urethra. By utilizing the normal variation in position of these muscles, in response to changes in intraabdominal pressure, compression of the urethral lumen is automatically increased at the exact times when it is most necessary in order to prevent leakage of urine.

CASE REPORT

The case that I wish to report is that of Mrs. M. McD. (Hospital No. 35233), 53 years of age, and of medium weight and stature. Her past history revealed nothing of importance with the exception of conditions which had occurred incidental to her pregnancies.

During thirty years of her life, she had a rather remarkable experience from the obstetric and gynecologic point of view. Between the ages of 23 and 41 years, a period of 18 years, she had 14 pregnancies. The patient may be excused for loss of memory regarding the details of some of her deliveries, but so far as could be determined from her statements and the available hospital records, the outcome of her pregnancies was as follows:

1. Six full-term pregnancies with one forceps delivery and five spontaneous deliveries.
2. Two premature, spontaneous deliveries at five months' gestation.
3. Five spontaneous abortions.
4. A laparotomy with removal of one tube for ruptured ectopic pregnancy.

The birth weights of 5 of her full-term babies ranged from 8 pounds 11 ounces to 9 pounds 9 ounces.

At 34 years of age, after her fifth full-term pregnancy, she had a vaginal plastic for birth injuries and an operation for retroversion. At 47 years of age, a complete vaginal plastic operation was done at a hospital in Flushing, Long Island. At the same time, the body of the uterus was removed by supravaginal hysterectomy for fibroids. This operation failed to relieve her chief complaint of incontinence of urine.

Four years later, at 51 years of age, another complete vaginal plastic was done at the Woman's Hospital. Following this operation, the anatomic result appeared to be excellent but her most troublesome symptom, incontinence of urine, still persisted.

On June 17, 1941, she was readmitted to the Woman's Hospital for the combined vaginal and abdominal operation described in this report. She was catheterized during the first three postoperative days. From then until her sixteenth postoperative day, when she was discharged, recovery was quite uneventful. She was continent and remarkably free from any bladder symptoms. Now at nearly eight months following this operation, the anatomic result appears to be good. The patient declares that she has had no leakage of urine since the day of her operation and that she is entirely free of any bladder symptoms.

From the patient's statements she had incontinence of urine continuously for 29 years. It began as stress incontinence following delivery of her first baby by forceps at 23 years of age, and finally relieved by the operation described at 52 years of age. Following the birth of her last baby at 37 years of age, she had constant leakage both day and night

and for this reason rarely left her home. She was unimproved following the two vaginal plastic operations at 47 and 51 years of age, but declares that her last operation was a complete success.

In conclusion it may be stated that:

1. A woman who, through loss of urethral sphincter control, had had partial urinary incontinence for twenty-nine years was cured by a new surgical technique after two vaginal plastic operations for the same condition had failed.

2. The new surgical procedure was devised primarily for the relief of urinary stress incontinence. It may prove to be of value as a step toward developing urinary continence whenever it is necessary by plastic surgery to construct a urethra that is absent as a result of congenital malformations or destructive birth injuries.

3. Ultimate success of the new procedure which has been described must depend upon whether the mechanical and surgical principles involved are sound.

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DISCUSSION

DR. THOMAS C. PEIGHTAL.—Dr. Aldridge has devised an admirable means by which the newly constructed periurethral fascia support is re-inforced at the point of greatest strain on the sutures. Thus, for instance, by his rectus fascia sling, the Kennedy operation may be strengthened at the weakest area where the tissues beneath the midurethra most often break down. This is a notable advance in the surgery of stress incontinence and we shall do well to utilize it.

DR. GEORGE F. HOCH.—Dr. Aldridge and I had a patient in common who had two unsuccessful attempts at correction. After the second operation a mass of scar tissue along the urethra acted as a barrier. For a time the result was perfect but soon this tissue disappeared and her incontinence returned. What caused this change? Very likely poor blood supply of this devitalized tissue. The use of live tissue should correct this error.

I believe in all these conditions teamwork between the gynecologist and urologist should decide whether the patient is suffering from an incontinence or an urgency secondary to some urologic disease, before any operative procedure is done. It may prevent some unsuccessful operations.

DR. BENJAMIN P. WATSON.—I am especially interested in the technical aspects of this procedure.

I and some others saw Dr. Miller do one of those fascial support operations, using vertical strips from the two recti muscles; it is quite a formidable procedure. I was impressed by the simplicity of Dr. Aldridge's transverse incision technique, taking two fascial strips laterally from the rectus sheath.

ADENOMYOSIS OF THE FALLOPIAN TUBE*

DONALD H. WRORK, M.D., AND ALBERT C. BRODERS, M.D.,
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THE distinctive morphologic characteristic of adenomyosis of the oviduct is the presence within the entire circumference of a thickened segment of myosalpinx of multiple, tubular, small caliber diverticuli of the tubal mucosa. While the process may involve the entire length of the tube, it is usually confined to the most medial segment of the tube. Fixed specimens of oviducts from 87 women who had the disease on one or both sides have been examined during the course of this study, the chief purpose of which is to consider its surgical significance.

Adenomyosis of the tube is an entity distinct from serosal endometriosis, by which term is meant the presence on the pelvic serosa of an endometrial adenosis (endometrium-like mucosal stroma with epithelium of either tubal or uterine type). This study is not concerned with this latter disease. A summary of the differences between the two conditions is presented a few pages hence.

DESCRIPTION

For 81.4 per cent (S.E.† ± 4.2 per cent) of 86 of the cases studied, the tubules penetrate the entire thickness of one or both myosalpinges (Table I). The epithelium of these glandlike structures is tubal in type

TABLE I. LOCATION OF THE TUBULES OF ADENOMYOSIS TUBAE AS SEEN IN CROSS SECTIONS TAKEN THROUGH THE CENTERS OF INVOLVED SEGMENTS

LOCATION	CASES		PER CENT	
Panmural	70		81.4	
1. Transmural continuity of epithelium of main tubal lumen with overlying serosa (tuboperitoneal fistulas)		19*		22.1*
2. Subserosal, without apparent serosal continuity		51*		59.3*
Midmural (inner half of musculature)	13		15.1	
Inner mural (subluminal)	3		3.5	
Total	86		100	

*It is probable that study of serial sections would have augmented these figures appreciably.

for almost all of the specimens studied; rarely is it uterine in type. It usually is ciliated. There is occasionally a single sharp-pointed pro-

*Abridgment of section on "Adenomyosis tubae" of thesis submitted by Dr. Wrork to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Surgery.

†Standard error, calculated by use of the formula

$$\text{S.E. } (\pm \text{ per cent}) = \sqrt{\frac{A \times (100\text{-}A)}{n}} \text{ where}$$

A is the percentage under discussion, and
n is the number of cases in that series.

trusion of the mucosa within the tubule which is without secondary folds; such a structure may represent a rudimentary endosalpingeal plica.

The junctions of these intramural tracts with the main tubal lumen are commonly right-angled. As such a tubule approaches the main tubal lumen, its caliber diminishes and it communicates by means of a narrow neck with the main canal, entering between two of the plicae. Concerning their course through the musculature, Rosenberger[18] has published the only drawing to be found among the previous writings on the subject depicting the course of such tubules as seen in a longitudinal section of an oviduct involved by adenomyosis. Their interlacing course, with occasional enlargements at their infrequent junctions with one another, is illustrated.

Although varying from one to 100 for the oviducts of 82 women, an average of 22 canals per cross section (each tubule cut several times) was found on study of sections taken through the centers of segments involved by adenomyosis.

An excessively thick and irregularly arranged myosalpinx is present in the segment involved by adenomyosis for 89 per cent of 72 of these instances (Table II). The distribution of the size of adenomyotic

TABLE II. MUSCLE COMPONENT OF ADENOMYOSIS TUBAE

TYPE*	QUANTITY OF MYOSALPINX	CASES	PER CENT
1	Not perceptibly increased	8	11.1
2	Slightly increased	19	26.4
3	Considerably increased	41	56.9
4	Very abundant muscle	4	5.6
	Total	72	100.0

*Type 1 is properly designated as adenosis; adenomyosis is the most accurate name for the remainder and the best collective name for the group.

TABLE III. SIZE OF THE CLASSIC TYPE OF ADENOMYOTIC NODULES (AT TUBOUTERINE JUNCTION) FOR FORTY-FOUR OF THE FIFTY-FOUR INSTANCES

SIZE, CM.*	CASES
1 by 0.5	2
1 by 0.7	7
1 by 1	18
1.5 by 1	11
2 by 2	4
3 by 2	1
5 by 2	1
Total	44

*The first figure represents the axial length of the lesion, and the second figure its diameter at the largest point.

nodules is given in Table III. The enlargements of the tube, which are due chiefly to an increase in the muscle component, are often symmetrical, and the process is often bilaterally symmetrical. Usually, although not necessarily, the increase in the quantity of tubal muscle bears a roughly quantitative relation to the number of tubules seen on cross section. Serial sections may demonstrate an isolated tubule in specimens suspected of representing a thickened myosalpinx only, although the thickened muscle may be present alone as a prominent uterine cornu (not a bicornuate uterus). For adenomyotic regions of the tube there is a less distinctive separation of longitudinal and circular muscular lamellae than is normal; in some instances the musculature is grossly irregular (Fig. 1).

Adenomyosis tubae was found to be bilateral for 83 per cent and unilateral for 17 per cent of 53 cases in which complete pathologic examination of the oviducts was possible (S.E. ± 5.2 per cent).

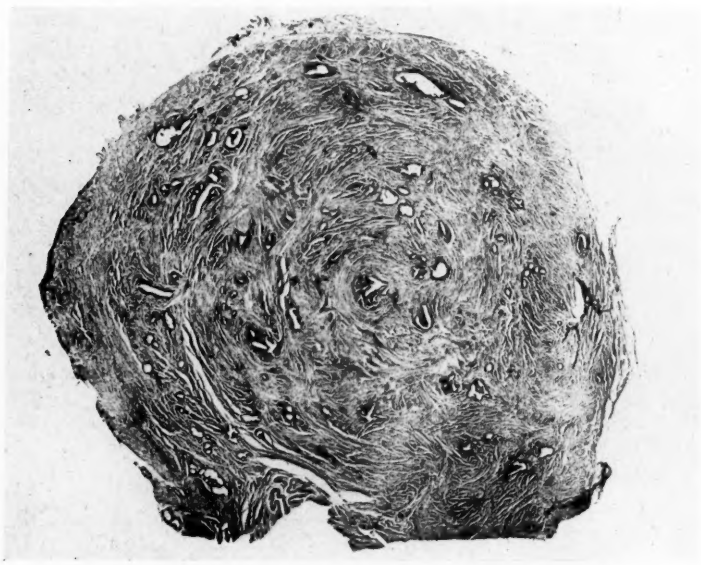

Fig. 1.—Cross section through isthmus of oviduct involved by adenomyosis. The irregularity of the muscle and the panmural distribution of the tubules are typical of most such specimens (×7).

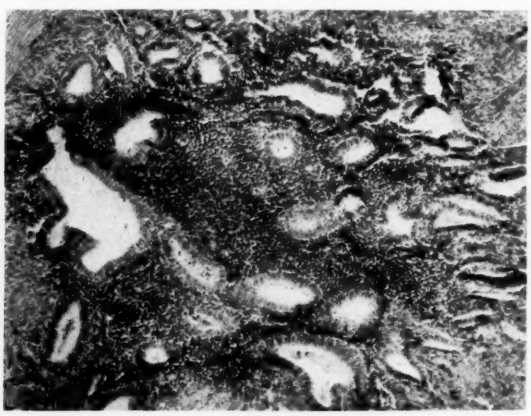

Fig. 2.—Cross section of central portion of oviduct of a single woman, 49 years of age, operated upon because of leiomyoma uteri. Bilaterally symmetrical adenomyotic segments in the tubal isthmuses, bilateral hematosalpinx with endometrium-like stroma beneath a portion of the tubal epithelium. The largest canal is the main tubal canal (×80).

Another phase of this study is concerned with an endometrium-like mucosal stroma which was found to be associated with adenomyosis tubae for 70 per cent of 81 cases of adenomyosis tubae (S.E. ± 5 per cent). Among such specimens the tubal type of mucosal stroma predominates,

the endometrium-like endosalpinx being present focally throughout them; it more often surrounds the epithelium of the tubules than it does that of the main tubal canal (Fig. 2). The question whether this condition adenomyosis, or their concurrence possesses the greatest significance has not been settled.

ORIGIN

There are three principal hypotheses of the origin of internal Muellerian adenomyosis: (1) that it is the result of inflammation, (2) that it is congenital, and (3) that it represents a blastoid growth of epithelium from a normally placed Muellerian mucosa.

Dougal[3] stated that adenomyosis tubae was known as an entity for at least fifty years before the contribution of von Recklinghausen[17]; however, little interest was shown in the condition until the appearance of the latter's monograph in 1896. He was reminded of the mesonephron by these structures, believing that some of them represented Henle's loops and glomeruli. He called such fusiform enlargements of the medial isthmus "tubal angle adenomas" (Wolffian). Pick, Kossman and Lockstedt (quoted by Villard and others[21]) lent their support to the belief that the tubules arose from the Wolffian body. By means of an embryologic approach, Meyer demonstrated this hypothesis to be untenable.

Chiari,[1, 2] one of the first to write on the subject, contributed the term, "salpingitis isthmica nodosa," which is used occasionally today. As his term implies, he considered the condition to be the result of foregoing salpingitis. After this idea had fallen into the discard during the years following Chiari's publication, von Franque (quoted by Dougal[3]) revived the hypothesis of an inflammatory genesis for adenomyosis of the tube. Meyer, the most able protagonist of this concept, stated his belief that the downgrowth of tubal mucosa was the result of hormonal and inflammatory stimulation, and that the increase in the muscular component of the structure was a form of hyperplasia in consequence of irritation about the penetrating growth of the tubules. Villard and others supported this view. In all, many contributions have been made, few in English.

Supporting the hypothesis of congenital origin, Schridde and Schoenholz, Lahm,[10, 11] Mestitz, and Weyeneth have made outstanding contributions. The last mentioned expressed his disagreement with Meyer's belief that adenomyosis tubae does not occur among newborn girls. Solutions for these problems, which require microscopic study of serial sections on a large scale, have not been settled yet unequivocally. Hoehne and Lehwirth have also made extensive studies on the subject.

In favor of the developmental (either congenital or postnatal), and opposed to the inflammatory genesis of adenomyosis tubae, the following evidence is available:

1. Adenomyosis is more common at the uterine ends of the oviduct, which inflammation touches lightly, than at the ampullar portion where the residue of inflammation is prominent.

2. There is no scar tissue to be seen around the usual adenomyotic tubule. When there has been previous salpingitis, its residue is more

obvious near the main tubal lumen than around the intramural adenomyotic tubules. Few of such tubules are found to be cystic, although cystic tubules might be expected to occur commonly if the causative process were inflammation. The narrow necks by which the tubules enter the main lumen cannot be interpreted easily as a formation likely to be the result of inflamation. Adenomyosis tubae is often unilateral in the presence of bilateral salpingitis.

3. Tubal adenomyosis is frequently bilaterally symmetrical. The hypothesis that it is the result of an inflammatory process does not account well for the high incidence of specimens showing similarity of size and position of nodules on the two sides.

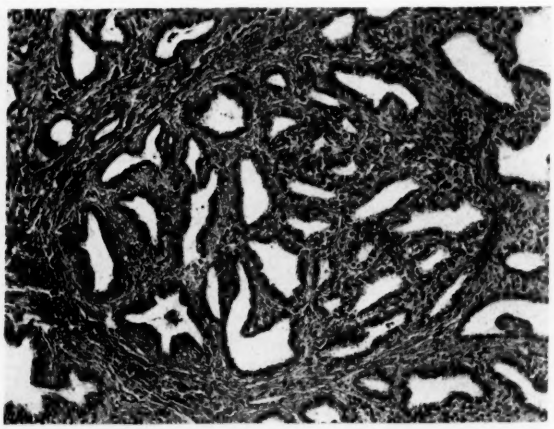

Fig. 3.—Cross section of center of lateral isthmus of an oviduct of a single woman, aged 28 years, operated on because of leiomyoma uteri, showing cribriform or lattice-like lumen of a type herein called congenital rather than adhesive, follicular, or pseudoglandular salpingitis. Elsewhere in such specimens were many regions of panmural adenomyosis. This condition was found alone only once (in control series); in other cases it was found with adenomyosis (present among 23 per cent of 58 cases of adenomyosis in Series 1 and 2). It was found among only two of the specimens showing both adenomyosis and tubal pregnancy. Tubal epithelium and tubal stroma were present throughout (×105).

4. There are more tubal anomalies among a series of specimens of adenomyosis tubae than among a comparable series showing evidences of chronic salpingitis. In 23 per cent of the 58 cases comprising Adenomyosis Series 1 and 2, a cribriform endosalpinx of the type shown in Fig. 3 was present. Segmental agenesia of the endosalpinx was present for 4, segmentally miniature lumen (a seventh of the normal diameter) for 1, and diffuse adenomyosis without a main tubal lumen for 6 of the specimens among these 58 cases. In all, in 41 per cent of 58 cases of adenomyosis tubae there was some other developmental anomaly of the tube on one or both sides (S.E. ± 6.5 per cent).

5. Unilateral adenomyosis tubae frequently is accompanied by homolateral adenomyosis uteri; the frequency of this concurrence has not been established. This situation suggests that there may be a predominant involvement of one of the two Muellerian canals of one person by the

process. Weyeneth first recorded an observation of this feature of the disease, and several such observations were made during the course of the present study.

6. Adenomyosis has a predilection for the tubouterine junctional zone of the Muellerian tract, just as other anomalies of the body (such as those of the enteron) have a predilection for transitional segments. Its incidence is thought to diminish caudad and craniad from the tubouterine junctional zone.

Sampson made a significant contribution to the study of the genesis of some types of adenomyosis tubae, as well as of serosal endometriosis. By means of studies of tubal stumps after salpingectomy he demonstrated that new tubules had grown from the previously ligated tubal mucosa ("endosalpingosis") among 76 per cent of 147 tubal stumps, whereas growth of new tubules was present among only 8 per cent of a control series of 200 specimens. As he indicated, this is excellent evidence that some of these lesions found in tubes not previously operated on may be acquired during adult life. Among the 118 control cases reported herein (194 oviducts) in 9 cases, or 7.6 per cent, adenomyotic regions were found on one or both sides. Sampson found, not only that the new growth of tubules from the tubal stump penetrated the adjacent myosalpinx, but that in some instances penetration of the overlying serosa occurred with involvement of the bowel (6 cases), the ovary (4 cases), or the abdominal wall after ventrifixation of the uterus (3 cases). For 2 specimens he found tubal pregnancy within the tubal stump, the result of canalization incident to the penetrating growth of the tubules. Since inflammation was present among 18 of the specimens studied by him, he interpreted the mucosal proliferation as probably having been initiated by inflammation and by the trauma incident to the salpingectomy.

The proximity of the most medial segment of the tube to the most rapidly regenerating tissue in the female body (endometrium during sexual maturity) suggests that the penetrating growth of adenomyotic tubules may be akin to the rapid regeneration of the mucosa of this adjacent segment.

There may be a relation between the absence of a muscularis mucosae and submucosae in the Muellerian tract, and the development of adenomyosis. In many regions throughout the oviduct the epithelium lies practically in contact with the myosalpinx, the lamina propria of the mucosa being extremely thin. A process similar to adenomyosis rarely if ever occurs among those hollow viscera having such layers intervening between muscle and mucosa.

In summary of this section it may be said that some instances of adenomyosis tubae are congenital, while others are acquired during adult life, and that the histologic characteristics of the lesion do not resemble those of lesions known to be the result of inflammation. During the course of this study no specimen was encountered which presented the characteristics usually associated with a postinflammatory picture. It is

not denied that such could occur; however, such an occurrence must be very uncommon indeed.

It is probable that the uterine mucosa and the juxtauterine endosalpinx (the middle Muellerian segment being the most highly differentiated portion of the tract) not only are more likely to be the sites of anomalies, but have a greater capacity than the upper and lower parts of the tract to react to any type of stimulation (physical, hormonal or inflammatory) by downgrowth of tubules. It is true that adenosis of the vagina and of the upper reaches of the oviduct is much less frequent than is the disease in the middle segment of the Muellerian tract.

DIFFERENTIATION OF "INTERNAL" AND "EXTERNAL" ADENOMYOSIS

The lesion under discussion here is the so-called "internal" type of Muellerian adenomyosis. By the "external" type generally is meant the presence in or on the pelvic serosa or other extragenital sites of regions of Muellerian mucosa. This is more properly a form of adenosis, since there is rarely any muscle growing with the ectopic endometrium-like tissue. Reference may be had to Table IV for other points of differentiation between the two conditions. Several instances wherein the two conditions existed concurrently have been encountered at the Mayo Clinic, in which instances it is possible that the serosal disease represented a transmyosalpingeal extension of the adenomyosis. Endometrium-like endosalpinx was present focally beneath the tubal epithelium of the "internal" tubules within these specimens. This will be discussed elsewhere.

TABLE IV. DIFFERENCES BETWEEN ADENOMYOSIS TUBAE AND SEROSAL ENDOMETRIOSIS

DIFFERENCES	ADENOMYOSIS TUBAE	SEROSAL ENDOMETRIOSIS
Synonyms found in study of the literature	Internal adenomyosis, internal endometriosis, endosalpingosis	External endometriosis, external adenomyosis, adenosis
Epithelium of tubules	Usually tubal type	Tubal or uterine
	In continuity with mucosa of main tubal lumen; occasionally with overlying serosa	Not in continuity with mucosa of main tubal lumen; closed or open to serosa
Length of tubules	Traverse radius of tube for 81 per cent of cases	Short or nonexistent
Location of tubules	Intramuscular	May invade muscle for short distance; not often on tubes
	Tubules mainly submucosal	Mainly subserosal or serosal
Mucosal stroma	Chiefly tubal type	Usually uterine type
Muscle component	Excessive and irregular	Absent; adenosis only
Patency of ostium	Closed more often	Almost always open
Dysmenorrhea	Rare	Practically always present

Some writers group adenomyosis and serosal endometriosis together under one heading, referring to them collectively as "ectopic endo-

metrium,'' ''Muellerianosis,'' ''adenomyosis'' or ''endometriosis.'' This no longer seems warranted in view of their entirely separate nature and significance.

PATHOLOGIC DIFFERENTIAL DIAGNOSIS OF ADENOMYOSIS TUBAE

Oviducts that are the site of chronic salpingitis may be so amazingly tortuous that an accurate cross section is difficult to secure. Cross sections of such specimens frequently cut through parts of the lumen several times, giving the impression that some of the canals are apart from the main tubal canal. Study of several nearby sections reveals the actual circumstance. The same is true for the occasional specimens having a bifurcated lumen.

Without serial sections it may be impossible to distinguish between adenomyosis and serosal endometriosis, since some specimens of adenomyosis tubae may have an endometrium-like mucosal stroma. Frankl[6-8] and Sampson have also made this observation.

On gross examination it may be impossible to distinguish a prominent uterine cornu from a cornual nodule of adenomyosis. There exists a cornual hyperplasia or thickening of muscle without adenosis; however, for such instances only serial microscopic study can exclude the presence of the adenosis component. As much as the entire isthmus may be characterized by an unusually heavy myosalpinx. Such specimens with or without epithelial tubules are often labeled ''hypertrophy'' of the oviduct.

At times adhesive endosalpingitis may be so severe as to leave an apparently glandlike picture on cross section. This has been called ''follicular'' salpingitis by Falk.[4, 5] That such instances are of inflammatory origin and are not adenomyosis is immediately apparent to one who has studied sections of specimens of both diseases. Fig. 3 is a section of a specimen having an anomalous type of endosalpingeal structure; we believe it does not represent a postinflammatory residue.

For the uterus the point at which the normal structure stops and adenomyosis begins often is not evident. However, since the epithelial boundary of the oviduct is rarely violated by that epithelium, it is justifiable to designate a condition as adenomyosis when the myosalpinx is invaded by the tubal epithelium.

Often some of the tubules of adenomyosis tubae are found to be segmentally cystic. This is especially apparent where endometrium-like mucosal stroma is also present in the specimens; this may result from localized occlusions due to sanguineous desquamate. The lining of such dilated tubules has the appearance of pavement epithelium and the picture reminds one of Wolffian tubules. Von Recklinghausen, who considered ''tubal angle adenomas'' to be Wolffian remnants, may have studied specimens containing these segmentally cystic tubules. Within such dilated tubules the presence of an intraluminal ''spur'' (rudimentary plica?) probably indicates that the lesion is of Muellerian

rather than of Wolffian origin. Certainly in many instances it is only by means of microscopic study of serial sections that one can distinguish between the two types of tubules.

For two oviducts nodules measuring 2 by 2 by 2 cm. have been found at the ampullar ends (Fig. 4). At the uterine extremities of both of these two specimens there was panmural adenomyosis. Both of these large nodules were filled with clotted blood and in each instance the cavity of the mass was in continuity with that of the tube. Such structures are commonly called "adenomyomas" although they do not have

Fig. 4.—Dorsum of uterus of a 59-year-old woman operated upon because of carcinoma of the endometrium. Right purulent salpingitis. The diameter of the uniformly thickened tube on the right is 8 mm., while that of the isthmus of the left is 5 mm. Diffuse adenomyosis throughout the right tube. The lumen of the mass measuring 2 by 2 by 2 cm. at the ovarian end of the right tube is in continuity with the main tubal lumen. One of the fimbriae may be seen at the lower pole of the mass. This sac contained clotted blood.

the structure of a true neoplasm. The mucosa within these two enlargements was for the most part absent, probably as the result of pressure necrosis. The wall of each, composed of heavy scar tissue, is a formation not seen among specimens of tubal pregnancy. They undoubtedly represent manifestations of the same process present at the medial ends of each of these two oviducts, similar to rectovaginoseptal "adenomyoma."

COLLECTION AND RECOGNITION OF SPECIMENS OF ADENOMYOSIS TUBAE

Table V shows the methods of selection of the several series of cases studied, and Table VI lists the primary reasons for operation among 87 patients who had adenomyosis tubae. Adenomyosis was present

TABLE V, A. SOURCES OF THE SPECIMENS OF ADENOMYOSIS TUBAE CONSIDERED HEREIN, WITH METHODS OF THEIR SELECTION BY SERIES

	CASES	TUBES	CASES AM.T.*
1. Tubal pregnancy series	100	116	13
2. Control series	118	194	9
3. Adenomyosis Series 1	18	33	18
4. Adenomyosis Series 2	40	71	40
5. Nongravid hematosalpinx series	45	71	7
Total number of cases of adenomyosis tubae			87

*Number of cases in which there was adenomyosis tubae on one or both sides.

TABLE V, B. METHODS OF SELECTION OF THE SERIES IN TABLE V, A.

1. Consecutive series of 100 cases listed in the file of the Mayo Clinic as "tubal pregnancy," restudied for the presence of adenomyosis of the oviducts.
2. A consecutive series of cases wherein the predominant pelvic pathologic picture was not tubal. The reasons for operation among these cases were approximately the same as are given in Table VI for the 87 cases of adenomyosis tubae.
3. Specimens of adenomyosis of both tubes and uterus collected during a brief pathologic study of adenomyosis uteri, not previously recognized as also containing regions of tubal adenomyosis.
4. Previously recognized and filed as adenomyosis tubae.
5. Consecutive cases listed in the file of the Mayo Clinic as "hematosalpinx without tubal pregnancy," where the hematosalpinx was listed as an incidental finding.

TABLE VI. PRIMARY REASON FOR OPERATION* FOR 87 CASES IN WHICH ADENOMYOSIS TUBAE WAS ALSO DISCOVERED AT PATHOLOGIC EXAMINATION

	CASES
Carcinoma of the fundus uteri	4
Menorrhagia	16
Sterility	3
Residue of pelvic inflammatory disease	9
Leiomyoma uteri	26
Enlargements of the ovaries	7
Endometriosis†	1
Tuboovarian abscess	3
Tubocutaneous sinus	1
Prolapsus uteri	2
Tuberculous salpingitis	2
Tubal pregnancy	13
Total	87

*Pathologic diagnoses given wherever practicable.
†Total incidence indeterminate.

among 13 per cent (S.E. ± 3.4 per cent) of a series of 100 specimens of tubal pregnancy, while 9 women having adenomyosis tubae were discovered among the control series of 118 cases (7.6 per cent S.E. ± 2.4 per cent). The majority of these specimens had not been recognized previously as containing adenomyosis. Because of the method of selection of the control series, it is reasonable to suspect that 5 to 10 per cent of removed pairs of oviducts (and those of the general female population) contain adenomyosis. This must be true unless the disease is associated more frequently with leiomyoma uteri or other surgical conditions of the pelvic organs, in which event its true incidence would be

somewhat lower. The exact frequency of their association has not been established.

The relatively high incidence of concurrence of leiomyoma uteri and tubal adenomyosis noted here and mentioned in the relevant literature is apparent rather than real. Surgically removed tissue showing both conditions is available for study because of the uterine tumor; however, cases were selected for this study solely because of the presence of adenomyosis tubae. Although the exact incidence of adenomyosis tubae among specimens of uterine leiomyomas is not at hand, it is apparent that the figure is much lower than the 30 per cent incidence of uterine leiomyomas among specimens of adenomyosis tubae which is noted here (Table VI), the height of this figure being due to the method of selection of cases for study.

Table VII shows numerically that most of the oviducts studied here which had been recognized previously as containing adenomyosis were cornual in location. Those newly discovered during the course of these examinations were particularly those wherein the enlargements were not obvious grossly, or for which the disease was diffusely distributed over the tubes and which therefore closely resembled specimens that were the site of salpingitis.

The recognition of the disease at laparotomy is greatly aided if one considers any irregularity, unusual firmness or apparent scarring of the isthmic segments of the tubes as very probably being adenomyosis. Thickening of the isthmus, if markedly at variance from the texture of the remainder of the oviduct, is quite likely to be due to adenomyosis. Tissue in situ that is the site of the disease is remarkable chiefly for its

TABLE VII. DISTRIBUTION OF ADENOMYOSIS TUBAE ALONG THE OVIDUCT

LOCATION	ADENOMYOSIS SERIES 2*		REMAINDER OF 83 CASES*	
	NO.	PER CENT	NO.	PER CENT
1. Entire oviduct	1	2.6	4	9.1
2. Ampulla only	0	0	1	2.3
3. Entire isthmus	2	5.1	8	18.2
4. Midisthmic	0	0	5	11.3
5. Medial isthmic only	0	0	8	18.2
6. Cornual	36	92.3	18	40.9
Totals	39	100.0	44	100.0

*These two columns are presented separately in order to show that the more diffuse type of the disease is not ordinarily recognized as such. Series 2 (see Table V), previously recognized and filed as such, is mainly constituted by the classical nodose enlargement near the tubouterine junction. Only 39 of 40 instances in Series 2 are included here because previous study of one specimen made the actual location of the disease uncertain.

The right column describes the location of the disease for 44 of the remaining 47 cases studied, 3 being omitted here for the reason given in the preceding paragraph. These specimens which had not been previously recognized as containing regions of adenomyosis were taken from the remainder of the series listed in Table V.

Where bilateral, the disease was symmetrical except for a few instances.

"Cornual" (No. 6 in the table) refers to the zone of the tubouterine junction of the tube.

This table does not show the comparative frequency of the cornual and the diffuse types because the methods of their selection were not comparable. It is felt, however, that the diffuse isthmic type is more common than the classical form of the disease.

resilient firmness, reminiscent of the texture of a mammary fibroadenoma. Isthmuses thickened as a result of a foregoing inflammation invariably present irregular angulations, but the resilient firmness characteristic of the usual type of adenomyosis is missing. Adenomyotic oviducts may be nodulated but are rarely markedly angled, and are quite likely to be similarly affected bilaterally.

The gross recognition of the disease in newly removed (unfixed) tissue may be difficult because of the great care required in order to accomplish a satisfactory gross examination of a cross section. Where specimens are opened axially, as is customarily done, the multiple false passages in the adenomyotic segment which usually are made by the scissors discourage its recognition. After such axial opening of the tubes, the openings of the tubules into the main tubal lumen are too small to be seen; and unless there is thickening, the disease may not be suspected. Sometimes the critical (for most instances of adenomyosis) medial tubal segment is the site of a sanguineous extravasation due to the customary application of a hemostat at this point during removal of the tube.

Fixation of the tissue, followed by examinations of cross sections cut by a sharp knife, is a requisite for the satisfactory gross identification of the less obvious types of tubal adenomyosis. Wherever present, the more abundant musculature of the involved segment is apparent, and the tubules, cut obliquely in the course through the musculature, may be seen as small gray areas, slightly different in color from the neighboring muscle.

PATENCY

Tubal patency in the presence of adenomyosis may be studied by the following methods: (1) extensive microscopic study of serial sections; (2) transtubal injection of fluid of fairly low viscosity using newly removed (unfixed) tissue (the simplest of the methods but one that is rarely used because the disease is infrequently recognized before fixation or axial opening); (3) postoperative tubal insufflation studies or salpingograms done "from below" after the disease has been recognized (but left untouched) at laparotomy.

For the tubal segments involved by adenomyosis studied by serial sections during these examinations, the tubal lumen has been seen to pass, compromised but uninterrupted, through most of the segments involved by adenomyosis. Obstruction was demonstrated by gross examination in only a few instances. It is reasonably certain that all of the specimens in which there was obstruction were not identified. Without serial sections for all specimens, the appraisal of the frequency and nature of such obstructions is limited. The majority of segments seem to be patent despite the high incidence of sterility (64 per cent of 39 married women having the disease in both tubes; S.E.±7.7 per cent).

Certainly there is no agreement in the related literature concerning the patency of the tubal canal within adenomyotic segments.

On several occasions during this study, corpora amylacea have been observed within the adenomyotic tubules throughout the myosalpinx. For one specimen a collection of these bodies completely blocked the tubules, as well as the main tubal lumen at one point. The epithelium of tubules frequently disappears near such foreign bodies (pressure necrosis), leaving these bodies deep in the musculature some distance from the nearest intact tubule. For such instances, foreign body giant cells are often present so that the general aspect on microscopic examination may be that of a pseudotubercle.

Fig. 5.—Infundibular tubal pregnancy: detached fetus and placenta at right. The nodose enlargement at the uterine end of the tube is a region of adenomyosis tubae measuring 10 by 8 by 10 mm. A section taken between this nodule and the uterus demonstrated a normal intervening segment of tube. This is a classic example of the disease sometimes called "salpingitis isthmica nodosa."

Other specimens of tubal adenomyosis for which obstruction of the lumen was known to exist are four specimens having segmental agenesia of the endosalpinx, one case having the lumina of the medial thirds of the tubes completely filled by endometrium, and six specimens in which no main lumen was discernible on study of cross section, the centers of the organs being riddled with adenomyotic canals.

In the study of the gravid oviducts which were found to contain regions of adenomyosis (13 of 100 cases of tubal pregnancy), no anatomic obstruction of the lumen could be proved or disproved without the aid of serial microscopic sections. That the adenomyosis present among these specimens may have been the cause or contributing cause of tubal nidation is suggested here not because of its presence among a greater percentage (13) that it was among the control series (7.6), since the standard errors of these two percentages show that the difference between them is not statistically significant; it is suggested, however,

by the presence of the adenomyotic process in the tube at precisely the medial angle of the gravid sac for eight of these thirteen specimens, and within the wall of the sac for two other instances. For the other 3 (of the 13) the adenomyotic regions were located some distance medial to the pregnancy sac, as seen in Fig. 5.

In view of the apparent patency of the lumen for specimens of adenomyosis tubae in which there was tubal pregnancy, and because of the presence of the adenomyotic process at the medial angle of the gravid sac, suggesting a causal relation, one is led to consider other possible mechanisms by means of which adenomyosis might be responsible for tubal nidation.

Six of the 13 specimens of oviducts having both tubal pregnancy and adenomyosis also had duplication of the lumen of a length of 1 cm. or more. That this condition was not encountered among the other 74 cases of adenomyosis of the tube suggests that it may have been responsible for some of the instances of tubal nidation, although the mechanism of its action is as yet only a matter of speculation.

An unusually heavy myosalpinx is present in 89 per cent of cases of adenomyosis tubae (Table II); this may constitute the basis of an unusually high collapsing force for such segments. That spasm of oviducts not known to be the site of adenomyosis may play a part in sterility is not at all well established, but it is suggested by the decreased pressure required to initiate the transtubal insufflation of air following the administration of antispasmodic drugs (for cases in which this pressure has been found previously to be high). It has also been stated that pregnancy occasionally occurs among previously sterile women following the administration of such drugs.[14] The anatomy of adenomyosis tubae is such that a physiologic occlusion might be present at times owing to spasm of its heavier musculature, the latter often being five times as thick as that of the adjacent normal tube. Further knowledge concerning the relative importance of these alleged influences must come from a clinicophysiologic approach, chiefly recognition at laparotomy of obstruction of the lumen by means of insufflation studies done from within the abdomen.

Adenomyosis may exert an influence on the occurrence of tubal pregnancy in other manners. The influence of endometrium-like stroma in the tube (present focally among 70 per cent of 81 of these patients, S.E.±5 per cent) will be considered elsewhere. That the tubal anomalies so frequently associated with adenomyosis of the tube might be associated with dysfunction of its transport mechanism without obstruction is another possibility, critical evidence for or against which must be obtained from both pathologic and clinical studies.

Since the points of entrance or exit of adenomyotic tubules into the main lumen and onto the serosa are so small, the possibility of a zygote gaining access to one of the tubules from within the tube or from within

the peritoneal cavity seems remote, although Lash has published a photomicrograph of an ovum within such a tubule. That tubal pregnancy may occur in tubal stumps containing adenomyotic tuboperitoneal fistulas (where the ovum enters the tubule from the peritoneal cavity) has been shown by Sampson. This suggests that a current toward the uterus may be present within such tubules.

Owing to the minute size of the orifices of such tubules and to the indistensibility of fixed tissues, the study of the ramifications of the tubules by roentgenologic methods after injection of radiopaque media into involved specimens is unsatisfactory for most instances. Sampson injected media into newly removed specimens and published a reproduction of a roentgenogram of such an instance. He was also able to inject a colored medium into such specimens which could be discerned in microscopic preparations. For one published specimen, this medium was shown to pass from the tubal lumen through the tubal wall and into an adherent ovarian hematoma.

The severity of inflammation in oviducts which are the sites of adenomyosis is sometimes greater than normal. Since any inflamed oviduct is likely to be removed surgically when encountered at operation, a fair answer to the question of just how conducive adenomyosis is to salpingitis is best had from study of instances of unilateral adenomyosis in which there is bilateral salpingitis. For accuracy, a considerable series would be necessary, for certainly there is great individual difference of structure of any two adenomyotic segments. Such pairs are uncommon. The impression gained from study of such instances is that the evidence of salpingitis is perceptibly more prominent on the side of the adenomyosis. The number and patency of tubules entering the main canal, the presence of endometrium-like endosalpinx, a heavier than normal myosalpinx, or of other anomalies, may all influence the course of an inflammatory process. Like an anomalous heart valve, oviducts with this anomaly may be more vulnerable to infection than normal oviducts. The relative importance of these various factors has not been assayed yet satisfactorily. Table VIII indicates the degree of leucocytic infiltration present within the adenomyotic segments in 65 of these cases.

TABLE VIII. CHARACTER AND AMOUNT OF LEUCOCYTIC INFILTRATION FOR 65 INSTANCES OF ADENOMYOSIS TUBAE

LYMPHOCYTIC INFILTRATION	CASES
None	13
Slight	18
Moderate	19
Considerable	5
Heavy	2
Purulent exudate present	8
Total	65

A gross estimation of the intensity of an instance of salpingitis is unsatisfactory here because of the thickened, nodular character of an adenomyotic segment.

Excluded from this compilation are specimens showing adenomyosis from the tubal pregnancy series (13), specimens showing tuberculosis (6), plus others considered indeterminate in this respect (3); total, 87.

The abundance of muscle noted in adenomyotic segments of tube, and the fact that the numerous epithelial processes (of considerable total length) may discharge their contents into a relatively short segment of

Fig. 6.—The lower half of the figure is the periphery of the oviduct while the upper portion is a flap of serosa capping a tubule which has penetrated the myosalpinx. Serial sections showed this tubule to be in continuity with the tubules below, which in turn are in continuity with the main tubal lumen at the isthmus (×90).

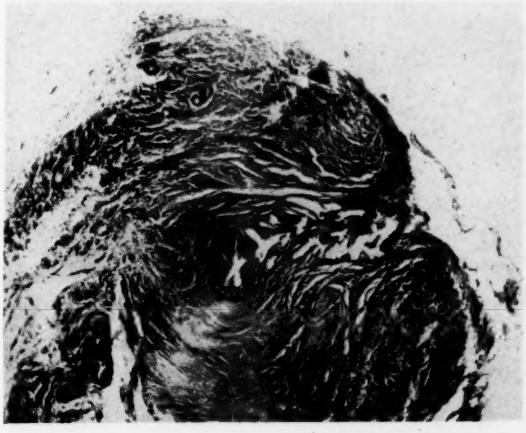

Fig. 7.—Cross section of the medial portion of an oviduct containing an adenomyotic tuboperitoneal fistula. The actual seromucosal junction is not seen in this section; it was located a few sections distant. No serosal endometriosis present; no endometrium-like endosalpinx present. The general aspect of this muscular anomaly is that of a failure of closure of two lips (×18).

tube, are factors which may interfere with the emptying of the organ. Blood or tubal contents discharged into such short segments conceivably could diminish the emptying capacity of the tube and protract an inflammatory process. As a contributing cause of salpingitis, the type of

mucosal stroma about the tubules may prove to be of more importance than the configuration of the tubules themselves.

The fact that many of the tubules of adenomyosis tubae penetrate the overlying serosa (Figs. 6, 7, and 8) may be quite significant, since, if the normal ostium of the tube is closed, these secondary ostia may provide vicarious passage for air to the peritoneal cavity. Such fistulas could also conduct particles of endometrium, sperm, blood, ova, or radiopaque media. However, these tubules are small, often contain sanguineous debris, and pursue a serpiginous course through the myosalpinx. These conditions militate against the leakage of contents through the accessory ostia. For instances in which a severe inflammatory process is present within the tubules, pelvic peritonitis could occur without

Fig. 8.—Section of medial isthmus of oviduct showing junction of the mucosa of a tubule with serosa. The transition is sharp, as it is normally at the tips of the fimbria. Note muscular anomaly. Serial sections here proved the continuity of serosa with mucosa of the main tubal lumen (×115).

contaminants having traversed the lateral reaches of the tube. Furthermore, for instances in which endometrium-like mucosal stroma surrounds the tubules, and in which the internal openings of the tubules are occluded by debris or so angled as to be obstructed, small amounts of blood derived from the uterus, the isthmus of the tube, or the tubule might be found in the cul-de-sac of Douglas without having traversed the natural ostium of the tube.

Since a detailed description of such conditions can be had only at laparotomy, the acquisition of further information relative to the importance (or lack of it) of adenomyosis tubae will be greatly aided by its wider recognition at the time of operation and by accurate descriptions of operative findings by many observers.

Phillips, quoted by Dougal, has said that cornual "endometriosis" is a rare but important cause of unilateral dysmenorrhea. There is some reason to believe that the disease to which he referred may have

been adenomyosis tubae. Among the records of the present series of 87 women who had adenomyosis tubae, no history of unilateral dysmenorrhea has been encountered; in fact, these records are singularly free of mention of this symptom. No significant item has been found which would permit preoperative recognition of the usual form of the disease. Of course, prolonged sterility without discernible cause strongly suggests it, and isthmic obstruction as discerned in salpingograms likewise suggests adenomyosis tubae.

SURGICAL DISPOSITION

What shall a surgeon do on encountering the disease at operation? If the uterus is to be removed for another reason, the question of salpingectomy resolves itself easily. For women past the childbearing age, having otherwise normal genitals, no evidence is provided by this study which might suggest that removal of the tubes is justified for the simple fact that adenomyosis is present. Where pain is the primary reason for laparotomy, removal of adenomyotic oviducts can hardly be expected to be of aid in the light of the infrequency of history of dysmenorrhea among the women whose oviducts have been studied here. The question of whether or not adenomyosis of the uterus causes painful menstruation is outside the scope of this study.

If the operation is undertaken on a woman who desires children, the problem is not so simple. It is imperative that proper distinction be made between chronic salpingitis and adenomyosis, since some apparently hopeless oviducts which are the site of adenomyosis are patent. After the injection of procaine into the regions of the hypogastric ganglia and along the uterine and ovarian arteries (intended to minimize isthmospasm), tubal patency may be tested from within the abdomen by means of a syringe and needle. If one or both tubes are patent (where the disease is encountered incidentally), the tubes are best left untouched, for although the incidence of sterility of married women of this series of cases (where both tubes were involved) was 64 per cent, that following tubal resection with reimplantation or the Estes operation is considerably higher. If these operations were more generally successful, indications for their performance might be more liberal. However, where there has been sterility of long standing, reimplantation undoubtedly offers more hope of temporary patency than does leaving the lesion in situ.

There is some evidence to indicate that women who have adenomyosis and whose oviducts are patent on one or both sides are more likely to experience tubal pregnancy than are women who have no tubal adenomyosis. Whether this risk is accepted may reasonably depend on the attitude of the patient as determined before operation. When the isthmus of one tube is obstructed and when its mate is open, it is likely that tubal pregnancy will be less probable if the adenomyotic tube is excised.

If the residue of inflammation is evident about the tubal fimbriae, it is probable that the isthmus of that tube is open; in this event the problem is not concerned with adenomyosis, but rather with the advisability of a plastic operation on the tubal ampulla or the Estes operation. The low incidence of pregnancy subsequent to procedures of this type is well known. Here is a fertile field for study.

At present it is sufficient to state that the only indication for a reconstructive operation for adenomyosis tubae is in the event of a patient who wants children, who already has experienced a reasonably long period of sterility, and on whom tests of patency done from within the abdomen have demonstrated isthmic obstruction on both sides. If the medial segments of the tubes only are involved, a reasonable course consists of segmental resections with reimplantations, followed by frequent postoperative insufflations "from below." Where the entirety of each tube is involved by adenomyosis, or where both tubes are hopelessly obstructed, the Estes operation is the only procedure offering any hope at all for pregnancy.

There is no reason to believe that adenomyosis of the tube undergoes malignant degeneration in other than extremely rare instances.

As has been pointed out by others, the propensity of adenomyotic tubules to grow from a tubal stump and to penetrate the tubal wall suggests again the need for excision of the intramural portion of the tube when salpingectomy without hysterectomy is undertaken.

SUMMARY

The classic form of adenomyosis of the tube is characterized by the presence in a firm and thickened segment of medial tubal isthmus of multiple, small, tubular diverticuli of the endosalpinx which pursue a serpiginous course through the tubal wall. The disease is bilateral for about 85 per cent of the cases studied herein.

The diffuse form of adenomyosis tubae, probably the more common type, is not identified as often as is the localized form, which is characterized by a nodose isthmus. This is true at operation because of the tendency of most surgeons to consider most types of tubal disease to be postinflammatory states (which this condition closely resembles). It is also true at gross pathologic examination because the customory method of such examination consists of axial opening of the organ by scissors. This maneuver leaves the disease difficult to discern. In situ, the presence of a resilient, firm segment of isthmus, with or without enlargement of that portion (where the ampulla is within normal limits) usually suffices to identify the disease. At pathologic examination, cross sectional study after fixation is the method best suited for identification of the less obvious type.

Evidence is submitted which suggests that the disease may not be a result of inflammation. Not the least of this evidence is the rather

high incidence of other tubal anomalies among specimens of adenomyosis tubae.

For 65 to 75 per cent of 81 cases, a mucosal stroma resembling endometrium rather than endosalpinx has been encountered focally beneath the tubal type of tubule lining. This stroma will be described separately.

For 39 married women who had the disease on both oviducts, the incidence of sterility was found to be 64 per cent (±8 per cent*). The mechanism of this feature of the disease is not well understood; several possible mechanisms have been suggested.

Adenomyosis tubae does not cause dysmenorrhea, although adenomyosis of the uterus is widely held to do so. The frequency of association of adenomyosis tubae and adenomyosis uteri has not been determined.

The tendency of the tubules of adenomyosis tubae is to penetrate the myosalpinx and overlying serosa with formation of multiple tuboperitoneal fistulas. These channels, although small, may provide vicarious passage for sperm, ova, blood, bacteria, opaque media used for diagnosis, or endometrial particles between the tubal lumen and the peritoneal cavity.

Adenomyosis tubae was discovered among 13 per cent (±3.4 per cent*) of specimens of tubal pregnancy, and among 7.6 per cent (±2.4 per cent*) of a control series. Where these two conditions are associated in one specimen the adenomyotic process often involves the tube at precisely the medial angle of the pregnancy sac.

Adenomyosis of the tube is suggested clinically by a long period of sterility without apparent cause, and by isthmic obstruction as seen by salpingogram.

The aim of this presentation is the stimulation of widespread recognition of the disease so that problems concerning the patency of tubes in which it is present, as well as many other problems, may be decided. It is probably present among 5 to 10 per cent of the general female population. Further information concerning it awaits large-scale recognition, with clinical, pathologic and physiologic study of its relation to serosal endometriosis, endometrium-like endosalpinx, sterility and many other problems.

It is likely that little will be accomplished surgically for the condition until there is improvement in the technique of tubal resection and reimplantation.

It is felt that the disease may be more significant than is generally recognized.

A discussion of its surgical disposition is included.

*Standard error.

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DOES THE ANTENATAL USE OF VITAMIN K PREVENT HEMORRHAGE IN THE NEWBORN INFANT?*

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FOR the past three years there has been widespread interest in the study of vitamin K as an agent for the prevention and treatment of hemorrhage in the newborn infant. There have been numerous reports[1] indicating that in infants whose mothers receive vitamin K a few hours before delivery and in infants who receive the substance immediately after birth, the blood prothrombin level is raised and the neonatal drop in prothrombin is greatly reduced or entirely absent.

In attempts to apply these findings clinically, there have been two reports[2, 3] in which vitamin K has been given to fairly large groups of women during labor. In each instance, the authors reported a definite reduction of neonatal hemorrhage in the infants whose mothers had received vitamin K as compared with those whose mothers were not so treated.

On the basis of these reports, we were stimulated to undertake a controlled study of the value of vitamin K given during labor in preventing hemorrhage in the newborn infants of a group of indigent mothers.

*Presented at a meeting of the Second Congress on Obstetrics and Gynecology, St. Louis, Mo., April 8, 1942.

PROCEDURE

Women admitted to the obstetric department of Gallinger Municipal Hospital are assigned alternately to the services of George Washington and Georgetown University Medical Schools. All patients are under the immediate supervision of one full-time obstetrician, one full-time pediatrician, and the same house staffs. With regard to the types of delivery, analgesia, and general obstetric and pediatric care, there is no appreciable difference between the two services.

From Oct. 7, 1940, to Jan. 17, 1942, mothers admitted to the George Washington service were given a single dose of 5 mg. of vitamin K* (2 methyl 1, 4 naphthoquinone) by mouth immediately after admission to the obstetric ward. Mothers admitted to the Georgetown service were used as controls. During the fifteen months of the study, approximately 140 women admitted to the George Washington service failed to receive vitamin K through an oversight of the attending physician or nurse. Since there was no intentional selection of these cases, they were added to the control group. There were 163 infants born to mothers whose records failed to indicate whether or not they had received vitamin K as ordered. This latter group was excluded from the series. Also excluded from the control and treated groups were: (1) All fetuses weighing less than 1,000 Gm. at birth; (2) 49 stillborn infants who showed no sign of life at the time the mothers were admitted to the hospital; and (3) 34 live-born infants who were delivered so soon after admission that no therapy could have been given to the mothers. All other infants born in the hospital are included in the series. The treated series comprises 1,151 infants whose mothers received vitamin K fifteen minutes to several days before delivery. The control series consists of 1,594 infants whose mothers received no vitamin K.

The infants of the treated mothers and the infants of those who served as controls were observed during their period of hospitalization for evidences of hemorrhage. Only grossly abnormal hemorrhage was considered; that is, definite melena neonatorum, hematemesis, continued bleeding from the cord after adequate ligature, gross subcutaneous or cutaneous hemorrhage, definite intracranial hemorrhage, or hemorrhage into the adrenal glands. These serious types of hemorrhage were recorded from clinical and post-mortem findings. Milder forms of hemorrhage such as vaginal bleeding, subconjunctival hemorrhage, cephalohematoma, or the vomiting of a small amount of brownish material shortly after birth were not included unless they were accompanied by other, more severe hemorrhagic manifestations.

In order to test the potency of the preparation used, microprothrombin tests were done on both mothers and infants by the method of Abramson and Weinstein.[4] In a group of unselected patients, the mother's blood prothrombin level was determined on admission. The determination was repeated on the mother's blood and on the cord blood at the time of delivery. In 30 untreated patients, the cord blood prothrombin level was approximately 15 per cent lower than the maternal blood prothrombin at the time of delivery. In 35 mothers who received 5 mg. of vitamin K by mouth, similar prothrombin determinations were made. The infants of mothers, treated at least four hours before delivery,

*Supplied by the Department of Medical Research, Winthrop Chemical Co.

showed a cord blood prothrombin level which was approximately 20 per cent above the cord levels of untreated patients.

In another small unselected group of infants from each series, blood prothrombin levels were done daily for the first week of life. Our findings coincided entirely with those previously reported;[1] that is, in normal untreated infants there is a marked drop in blood prothrombin level for the first three or four days, followed by a rise to normal. In infants whose mothers receive vitamin K four hours or more before delivery, this drop is much less pronounced.

The specific treatment of infants showing clinical evidence of gross hemorrhage consisted of the administration of oral or intramuscular vitamin K and of intramuscular or intravenous injections of blood as outlined in Tables IV and V.

RESULTS

The incidence of hemorrhage has been correlated with the period of hospitalization before delivery, the type of delivery, and the maturity of the infant as judged by the weight. Abnormal bleeding occurred in 22, or 1.4 per cent, of 1,594 infants whose mothers received no vitamin K and in 20, or 1.7 per cent, of 1,151 infants whose mothers received vitamin K on admission.

It is of interest to note that the incidence of hemorrhage is essentially the same as that reported in the control series of Hellman, Shettles, and Eastman,[2] and of Beck, Taylor, and Colburn.[3] If only the types of hemorrhage that we have included are considered from the totals reported by Sanford and his co-workers,[5] the incidence of abnormal bleeding in their total series is comparable to ours.

Table I shows the incidence of hemorrhage in infants with relation to the period of hospitalization and the administration of vitamin K to the mothers. There was very little difference in the percentage incidence of hemorrhage in those infants whose mothers received vitamin K a short while or a long while before delivery. Nine, or 1.8 per cent, of 509

TABLE I. INCIDENCE OF HEMORRHAGE IN INFANTS WITH RELATION TO THE PERIOD OF HOSPITALIZATION AND THE ADMINISTRATION OF VITAMIN K TO MOTHERS DURING LABOR

HOURS IN HOSPITAL BEFORE DELIVERY	MOTHERS RECEIVED NO VITAMIN K		MOTHERS RECEIVED VITAMIN K ON ADMISSION	
	NO. OF INFANTS	INFANTS WITH HEMORRHAGE	NO. OF INFANTS	INFANTS WITH HEMORRHAGE
Four or less	841	7 or 0.8%	509	9 or 1.8%
Over four through twenty-four	578	5 or 0.9%	526	8 or 1.5%
Over twenty-four	175	10 or 5.7%	116	3 or 2.6%
Total	1,594	22 or 1.4%	1,151	20 or 1.7%

infants born within four hours after the administration of vitamin K showed hemorrhage. There were 8 patients, or 1.5 per cent, with hemorrhage in 526 infants born between four and twenty-four hours after the mothers received the drug. In the treated series, among 116 infants who were born over twenty-four hours after admission, there were 3 infants, or 2.6 per cent, who showed hemorrhage. In two of these infants, the hemorrhage was definitely due to traumatic delivery (see Table V).

The greatest prophylactic value from vitamin K given orally is said to be obtained in infants born between four and twenty-four hours after the mothers have received the preparation. In our study of infants born in this time interval after admission to the hospital, 8, or 1.5 per cent, of the infants of treated mothers compared with 5, or 0.9 per cent, of the control infants, showed evidence of hemorrhage. This comparison indicates no reduction in the incidence of hemorrhage in infants born from four to twenty-four hours after the antenatal administration of vitamin K.

With reference to the infants born over twenty-four hours after admission, there is an apparent, but not statistically significant difference in the percentage of hemorrhage occurring in the treated and untreated infants. The difference can be accounted for, in a large measure, by the greater incidence of definitely traumatic deliveries in the untreated series (see Tables IV and V).

With regard to the administration of vitamin K after admission to the hospital, an analysis of all our data brings out a point of extreme importance from the public health and administrative standpoint. We have recorded information on 2,942 infants, a part of whom have not been used as controls or treated cases for reasons stated above. Of this group of 2,942 infants, 922, or 31.3 per cent, were born within two hours after admission and 1,479, or 50.1 per cent, were born within four hours after admission to the hospital. It is quite certain that oral vitamin K will be ineffective in raising the infant's blood prothrombin level when given to the mothers within two hours of delivery, and it is

TABLE II. INCIDENCE OF HEMORRHAGE IN PREMATURE AND FULL-TERM INFANTS WITH RELATION TO THE ADMINISTRATION OF VITAMIN K TO MOTHERS DURING LABOR

WEIGHT OF INFANTS	MOTHERS RECEIVED NO VITAMIN K		MOTHERS RECEIVED VITAMIN K ON ADMISSION	
	NO. OF INFANTS	INFANTS WITH HEMORRHAGE	NO. OF INFANTS	INFANTS WITH HEMORRHAGE
Premature infants (1,000 to 2,499 Gm.)	210	7 or 3.3%	132	6 or 4.5%
Full-term infants (2,500 Gm. or over)	1,384	15 or 1.1%	1,019	14 or 1.4%
Total	1,594	22 or 1.4%	1,151	20 or 1.7%

TABLE III. INCIDENCE OF HEMORRHAGE IN INFANTS WITH RELATION TO TYPE OF DELIVERY AND THE ADMINISTRATION OF VITAMIN K TO MOTHERS DURING LABOR

TYPE OF DELIVERY	MOTHERS RECEIVED NO VITAMIN K		MOTHERS RECEIVED VITAMIN K ON ADMISSION	
	NO. OF INFANTS	INFANTS WITH HEMORRHAGE	NO. OF INFANTS	INFANTS WITH HEMORRHAGE
Spontaneous	1,307	7 or 0.5%	923	13 or 1.4%
Forceps	180	7 or 3.9%	165	4 or 2.4%
Breech	79	5 or 6.3%	49	3 or 6.0%
Cesarean section	28	3 or 10.7%	14	0
Total	1,594	22 or 1.4%	1,151	20 or 1.7%

TABLE IV. ANALYSIS OF THE 22 INFANTS WHO SHOWED HEMORRHAGE FROM THE GROUP OF 1,594 MOTHERS WHO RECEIVED NO VITAMIN K

NO.	TYPE OF DELIVERY	WEIGHT (GM.)	TIME IN HOSPITAL BEFORE DELIVERY	TYPE AND TIME OF HEMORRHAGE	RESULT	REMARKS AND AUTOPSY FINDINGS
1	Low forceps	4,025	5½ hr.	Subcutaneous on the third day	Recovered	Prothrombin less than 10%. Vit. K 5 mg. orally. Prothrombin increased to 100 per cent. R.B.C. 2,700,000; transfusion
2	Spontaneous	1,985	2½ hr.	Generalized cutaneous third day	Died 14 days	Prothrombin less than 20%. Vit. K 6 mg. Transfusion. Bleeding stopped. Died 11 days later of infection. Had syphilis. No autopsy
3	Cesarean section	3,630	5 days	Gastric on second day	Recovered	On 10/13/41, prothrombin 8%. Vit. K 1.5 mg. orally. On 10/14/41, prothrombin 5%, Vit. K 1.5 mg. orally. 10/15/41, prothrombin 50%
4	Spontaneous	4,480	4 days	Gastric on first day	Recovered	Prothrombin 30%. Vit. K 2 mg. I.M. Four hours later prothrombin 44%
5	Breech	2,125	2½ hr.	Gastric on seventh day	Died 9 days	11/16/41, prothrombin 33%. Vit. K 6 mg. I.M. Prothrombin 80%. Bleeding stopped. Died 11/17/41. Clinical diagnosis pneumonia. No autopsy
6	Spontaneous	3,315	1¼ hr.	Gastric on third day	Recovered	Prothrombin not done. Vit. K 2 mg. I.M.
7	Spontaneous	3,175	11 hr.	Cord on first day	Recovered	Prothrombin not done. 20 c.c. whole blood intramuscularly
8	Cesarean section	1,560	9 days	Adrenal	Died at 6 days	6/16/41, bullous impetigo. Died on 6/17/41 with massive bilateral adrenal hemorrhage

9	Breech	1,415	3¾ hr.	Petechial at birth	Died 1 hr.	Petechiae in lungs, thymus, and heart
10	Midforceps	3,005	22½ hr.	Petechiae and intracranial at birth	Died intrapartum	Petechiae in heart. Cerebral hemorrhage. No rupture of vessels seen
11	Spontaneous	2,720	7 days	Intracranial at birth	Died intrapartum	Cerebral Hemmorage. No rupture of vessels seen
12	Breech	1,560	1½ hr.	Intracranial	Died 7 days	Diarrhea on fourth day. Prothrombin not done. Massive intracranial and intraventricular hemorrhage. No rupture of vessels seen
13	Cesarean section	2,130	20 days	Clinical intracranial at birth	Died 2 days	Prothrombin not done. Vit. K 2 mg. I.M. and 2 mg. orally. Transfusion. No post mortem
14	Low forceps	4,310	4 days	Intracranial at birth	Died 36 hr.	Ruptured cerebral vessels.
15	Version and extraction	5,370	3 days	Intracranial at birth	Died 19 hr.	Ruptured cerebral vessels. Adrenal hemorrhage
16	Midforceps	4,055	3 days	Intracranial	Died intrapartum	Ruptured cerebral vessels
17	Spontaneous	3,495	2 days	Intracranial	Died intrapartum	Ruptured cerebral vessels
18	Midforceps	4,990	2 days	Intracranial	Died intrapartum	Ruptured cerebral vessels
19	Midforceps	4,280	16¾ hr.	Intracranial at birth	Died 1 day	Ruptured cerebral vessels and hydrocephalus
20	Spontaneous	1,090	12 hr.	Intracranial	Died 6 hr.	Ruptured cerebral vessels
21	Midforceps	3,035	3 hr.	Intracranial	Died intrapartum	Ruptured cerebral vessels
22	Version and extraction	3,630	1½ hr.	Intracranial at birth	Died first hour	Ruptured cerebral vessels

TABLE V. ANALYSIS OF THE 20 INFANTS WHO SHOWED HEMORRHAGE FROM THE GROUP OF 1,151 MOTHERS WHO RECEIVED VITAMIN K ON ADMISSION

NO.	TYPE OF DELIVERY	WEIGHT (GM.)	TIME IN HOSPITAL BEFORE DELIVERY	TYPES AND TIME OF HEMORRHAGE	RESULT	REMARKS AND AUTOPSY FINDINGS
1	Spontaneous	1,445	32¾ hr.	Mouth, nose and anus. Second day	Died at 2 days	Prothrombin not done; slight bloody vomitus at 6 A.M.; Vit. K 2 mg. I.M. at 8:30 A.M. and at 9 A.M. Bleeding more profuse; died at 10:30 A.M. Hemorrhage into lungs and gastrointestinal tract
2	Spontaneous	3,215	17 hr.	Intestinal on third day	Recovered	Prothrombin not done. Vit. K 2 mg. I.M. and 6 mg. orally
3	Spontaneous	2,765	2¾ hr.	Intestinal on fifth day	Recovered	Prothrombin 100%. R.B.C. 1,000,000. Two blood transfusions
4	Spontaneous	3,680	2½ hr.	Intestinal on fifth day	Recovered	Prothrombin not done. Vit. K 4 mg. I.M.
5	Low forceps	3,030	19½ hr.	Gastric on second day	Recovered	Vit. K 2 mg. I.M. and 2.5 mg. orally; bleeding continued for 24 hours
6	Spontaneous	3,275	2¼ hr.	Gastric on first day	Recovered	Prothrombin 27%. Vit. K 2 mg. I.M. Two hr. later prothrombin was 95%
7	Spontaneous	3,780	1¾ hr.	Cord on first day	Recovered	Prothrombin 50%. Vit. K 3 mg. orally. Prothrombin next day was 64%
8	Breech	1,369	½ hr.	Adrenal at birth	Died at 5 hours	Cerebral edema and adrenal hemorrhage

9	Spontaneous	3,445	8½ hr.	Clinical intracranial. First day	Recovered	Prothrombin 56%; whole blood 20 c.c. I.M.
10	Spontaneous	2,720	21¾ hr.	Intracranial	Died intrapartum	Cerebral hemorrhage with no rupture of vessels found
11	Spontaneous	2,185	17 hr.	Intracranial	Died at 12 days	On eleventh day developed diarrhea and pneumonia. Prothrombin not done. Cerebral hemorrhage with no rupture of vessels found. Bronchopneumonia
12	Spontaneous	2,360	9¾ hr.	Intracranial	Died at 13 hr.	Prothrombin 21%. Vit. K 2 mg. I.M. Mild cerebral hemorrhage with no rupture of vessels
13	Low forceps	3,590	7½ hr.	Intracranial	Died at 5 days	Cyanotic from birth. Prothrombin 67%. Vit. K 4 mg. I.M. Cerebral hemorrhage with no rupture of vessels found. Aspiration pneumonia
14	Spontaneous	1,675	4½ hr.	Intracranial at birth	Died at 12 hr.	Subtentorial hemorrhage with no rupture of vessels found
15	Breech	3,145	2½ hr.	Intracranial at birth	Died at 6 hr.	Cerebral hemorrhage with no rupture of vessels found
16	Spontaneous	4,025	2 hr.	Intracranial	Died at 6 days	Died suddenly on sixth day. Bronchopneumonia and cerebral hemorrhage with no rupture of vessels found
17	Midforceps	3,290	6 days	Intracranial at birth	Died at 10 hr.	Prothrombin 14%. Vit. K 2 mg. I.M. Ruptured cerebral vessels and petechiae of pleura
18	Version and extraction	3,190	31 hr.	Intracranial at birth	Died intrapartum	Ruptured cerebral vessels
19	Midforceps	3,460	1 hr.	Intracranial and adrenal	Died intrapartum	Ruptured cerebral vessels and adrenal hemorrhage
20	Spontaneous	1,715	¾ hr.	Intracranial at birth	Died at 15 hr.	Ruptured cerebral vessels

doubtful that it will have much effect if given within less than four hours of delivery. At least one-third and probably one-half of our patients entered the hospital too late for the drug, administered immediately by mouth, to exert any influence. It is probable that this experience will be repeated in other large municipal institutions.

The relationship of the administration of vitamin K to the occurrence of hemorrhage in premature and mature infants is shown in Table II. In the control group, there were 210 premature infants with 3.3 per cent hemorrhage and 1,384 full-term infants showing abnormal hemorrhage in 1.1 per cent. The vitamin K treated series contained 132 premature infants with 4.5 per cent hemorrhage and 1,019 full-term infants with 1.4 per cent hemorrhage. While both groups showed severe hemorrhage about three times as frequently in premature as compared with full-term infants, there was no significant statistical difference in the percentage of hemorrhage occurring in treated and untreated full-term and in treated and untreated premature infants.

Table III shows no significant reduction in the incidence of hemorrhage in infants whose mothers received vitamin K with relation to the type of delivery. Hemorrhage was less in the control group of infants born by spontaneous delivery; the control infants born by forceps delivery and by cesarean section showed a slightly higher percentage of hemorrhage than in the treated series. The differences are not great enough to be of statistical significance.

A detailed analysis of the infants with hemorrhage in the two groups of patients is given in Tables IV and V. There was a striking similarity of the hemorrhagic manifestations in the two groups of infants with the single exception that rupture of the cerebral vessels was found as a cause of intracranial hemorrhage much more frequently in the control than in the treated group. In the treated group there were 12 and in the control group 13 infants with intracranial hemorrhage. In the control series, ruptured cerebral vessels were found to be the cause of hemorrhage in 9 infants; in the treated series, ruptured vessels were found in only 4 of the 12 infants with cerebral hemorrhage. Intracranial hemorrhage, without definite evidence of trauma, was found more frequently in the treated than in the untreated infants. In the two groups, there was no appreciable difference in the number of infants showing gastrointestinal, cutaneous, umbilical cord, or adrenal hemorrhage.

Among 1,594 infants whose mothers received no vitamin K, there were 78, or 4.9 per cent, fetal deaths. There were 47 deaths, or a fetal mortality of 4.1 per cent, among the 1,151 infants of treated mothers. Included in both groups are all infants showing evidence of life on admission, but dying during labor, and all neonatal deaths occurring within two weeks after birth. Since there were 31 autopsies in 47 fetal deaths (66 per cent) in the treated series and 55 autopsies in 78 fetal deaths (70.5 per cent) in the control series, the post-mortem findings in the two groups should be comparable. A complete list of the recorded causes of fetal deaths in both groups of patients is given in Table VI. Hemorrhage, not definitely due to trauma, was associated with approximately 10 per cent of the fetal deaths. Traumatic hemorrhage, anoxia, prematurity, congenital abnormalities, and infections continued to account for about 85 per cent of our fetal mortality.

None of the mothers showed any intolerance to vitamin K. Vitamin K seemed to exert no influence on the incidence of puerperal morbidity, thrombophlebitis, or maternal mortality.

TABLE VI. AN ANALYSIS OF FETAL DEATHS OCCURRING IN THE CONTROL AND IN THE VITAMIN K TREATED SERIES OF INFANTS

1,594 INFANTS WHOSE MOTHERS RECEIVED NO VITAMIN K			1,151 INFANTS WHOSE MOTHERS RECEIVED VITAMIN K ON ADMISSION		
Total number infants died	78	(4.9%)	Total number infants died	47	(4.1%)
Premature infants died	51	(65.4%)	Premature infants died	32	(68.1%)
Full-term infants died	27	(34.6%)	Full-term infants died	15	(31.9%)
Stillbirths	27	(34.6%)	Stillbirths	8	(17%)
Intracranial hemorrhage (Traumatic, 4)	6		Intracranial hemorrhage (Traumatic, 2)	3	
Anoxia	11		Anoxia	3	
Craniotomy	2		Craniotomy	1	
Congenital abnormality	1		Toxemia (eclampsia)	1	
Intrauterine infection	3				
Cause unknown	4				
Live births	51	(65.4%)	Live births	39	(83%)
Intracranial hemorrhage (Traumatic, 5)	6		Intracranial hemorrhage (Traumatic, 2)	5	
Infection	9		Infection (Intracranial hem., 3)	12	
Gastrointestinal hem.	1		Gastrointestinal hem.	1	
Congenital abnormalities (Intracranial hem., 1)	5		Cerebral edema	2	
Anoxia	6		Anoxia	3	
Prematurity (no other cause found)	23		Prematurity (no other cause found)	15	
Cause unknown	1		Cause unknown	1	

SUMMARY AND CONCLUSIONS

We have made a careful clinical analysis of gross hemorrhage occurring in the infants of mothers admitted to a municipal hospital. These mothers represent the lowest income group of a metropolitan area. It is reasonable to assume that dietary deficiencies and obstetric complications should be maximal in this group of patients. If these factors contribute materially to the occurrence of hemorrhage in the newborn, any procedure directed toward the reduction of neonatal hemorrhage should manifest its greatest benefits in patients of the lowest economic level such as we have studied.

A single dose of 5 mg. of vitamin K was given by mouth on admission to the mothers of 1,151 infants; the infants of 1,594 mothers who received no vitamin K served as controls. There was no appreciable ill effect of the vitamin on the mothers. As it was done in this study, the administration of vitamin K to mothers *had no evident effect in reducing the incidence of neonatal hemorrhage.* The vitamin K used was effective in raising the blood prothrombin levels of both the mothers and infants. If an elevated blood prothrombin level is a significant factor in preventing neonatal hemorrhage, we are unable to explain the results of our clinical survey. Additional clinical and laboratory studies involving large groups of patients should clarify this question.

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PREGNANEDIOL DETERMINATIONS IN GYNECOLOGY AND OBSTETRICS*

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MANY disturbances of gynecologic and obstetric functions have been related by fact or by theory to altered levels of progestin elaboration. Since objective and accurate definition of these levels still remains a diagnostic problem, much therapy employing progestin has been founded upon presumed rather than upon established functional pathology.

Venning's gravimetric method for determining urinary pregnanediol (a metabolic product of progestin),[1] described in 1937, aroused the hope that it would permit practical quantitations of progestin levels in clinical practice. During the past four years correlational studies designed to evaluate this method have been pursued by our group. In all 7,114 twenty-four-hour specimens of urine of 233 women have been quantified for pregnanediol. Conclusions regarding practical application of the method to gynecologic and obstetric practice are reported in this communication.

*Read by invitation by E. C. Hamblen at a meeting of the Washington Gynecologic Society, March 28, 1942.

METHODS FOR ASSESSING CORPUS LUTEUM FUNCTION

Numerous methods for determining the levels of corpus luteum activity exist. None is ideal for clinical application.

1. *Bio-assay Studies.*—These have yielded disappointingly few positive data. The reason is obvious: the specific pharmacologic potency of progestin is exhausted to a great degree by the time its products filter through the kidney. The result has been that urinary extracts yield little or no progestational activity when tested by diverse techniques: (a) the Corner-Allen rabbit method;[2] (b) a method which measures progestin's antiestrogenic, vaginal effects;[3] (c) the bitterling ovipositor test;[4] and (d) one which employs the intrauterine application of the extract to increase its sensitivity.[5]

2. *Vaginal Smears.*—The microscopic study of repeated vaginal spreads, suitably stained, has been described as indicating the occurrence of significant cytologic alterations during the menstrual cycle. Some clinicians are quite enthusiastic over this method as a diagnostic aid in quantifying estrogenic and progestational levels. Most gynecologists have not been able to secure by this method clear-cut diagnostic data which were translatable to the individual patients seen in their practices. The vagaries of the patient, in part due to vaginal and cervical infections, often render prolonged studies necessary to segregate pertinent fluctuations. Critical correlational studies of vaginal cytology with other objective manifestations of the menstrual cycle are altogether too few. The method has not been applied to the determination of progestin levels during gestation.

3. *Basal Temperatures.*—Reports have appeared which suggest that significant alterations occur cyclicly in basal temperatures, ovulation occurring at the time when the lowest temperatures prevail. Sufficient data are not available to permit just evaluation of this method for diagnosis of ovulation and, as a corollary, of corpus luteum function. One fears that a simple method, such as temperature taking, will not prove the solution to this diagnostic problem. Obviously this method would not be applicable to the grading of progestin levels during gestation.

4. *Endometrial Studies.*—The technique of endometrial biopsy is the only one of these methods which has permitted the practical acquisition of pertinent diagnostic data with regard to the level of ovarian function. The method obviously cannot be used during gestation.

When biopsies are secured within the first twelve to eighteen hours after the onset of bleeding, the endometrium usually serves quite reliably as a mirror of the total endocrine influences operative during the antecedent cycle. All data of this character deal with past history: they do not predict the future. When 2 or more consecutive ovarian cycles have been of anovulatory type, i.e., bleeding has occurred from estrogenic endometriums, it is compatible with reasonably accurate clinical thought to assume that the immediate future cycles, unless modified by therapy, will be of the same order. When specimens of endometrium are secured from 2 or 3 sites of the uterine lining at each examination, the criticism of inadequate sampling in part is circumvented.

Grading of the progestational response at the end of the cycle is possible, when biopsies are taken at the onset of bleeding. The degree of progestational response may indicate roughly the level of progestin secretion; it must be remembered, however, that this is modified also by

the degree of responsiveness and by the ability of effective utilization which characterize the endometrium. A simple system for the grading of progestational responses which was designed and is used by us follows:

M-, minimal and irregular (patchy) progestational response
M, moderate and irregular (patchy) progestational response
M+, marked but irregular (patchy) progestational response
P-, minimal (immature) but regular progestational response
P, normal progestational response
P+, marked (decidualike) progestational response

5. *Pregnanediol Method.*—Of the 4 types of studies discussed to this point, only the biopsy method has permitted practical application. For the most part, the endometrial data secured permit only qualitative information regarding ovarian function during nonpregnant cycles and are not available during the gestational cycle.

When Venning provided a gravimetric method for the estimation of the sodium pregnanediol glucuronide content of urine and when she and her associates[1] submitted evidence that this steroid-complex might represent a major metabolic product of progestin, the hope was aroused that this technique would permit an accurate, practical and quantitative means of estimating clinically progestin levels both in the nonpregnant and pregnant states.

Other methods for the estimation of urinary pregnanediol have been described by Veitsch and associates[6] and by Bachman and his group.[7] Our work[8] has been confined strictly to the employment of Venning's technique. Our faithful adherence to this technique has been favored by having a research associate during a part of our studies who was common to both groups (C. J. P.).

METHODS

The Venning technique has been described in detail by its author. Certain generalizations regarding it are judged to be pertinent to the present discussion.

The routine requires repeated and consecutive examinations of twenty-four-hour specimens of urine during the nonbleeding phase of the ovarian cycle to be sampled and continuous examinations of all twenty-four-hour specimens during the gestational cycle under study. Single determinations are of little value.

The technical details of the method are as follow: a four-fold extraction of the urine with normal butyl alcohol; evaporation to dryness under reduced pressure of the combined butyl alcohol extracts; solution of the residue in 0.1 N solution of sodium hydroxide; a three-fold extraction with butyl alcohol; evaporation to dryness under reduced pressure of the combined butyl alcohol extracts; precipitation by acetone of an aqueous solution of the residue; reprecipitation from fresh acetone; solution of the second acetone precipitate in hot 95 per cent ethyl alcohol; evaporation to dryness in a previously tared beaker; weighing of the residue; determination of melting point of the residue; calculation of the amount of steroid-complex content of total twenty-four-hour specimen of urine.

The cumbersomeness of this method is illustrated by the facts that a highly trained, efficient laboratory technician provided with adequate equipment can handle only the daily urines of 8 patients and that, since

four days are required for the completion of the quantitation on any one specimen, five days elapse from the time collection of a twenty-four-hour specimen of urine is begun until the final report on its pregnanediol-complex content is obtained.

All patients investigated had had complete gynecologic and endocrine surveys which included, as minimal requirements, basal metabolic determinations, roentgenograms of the sella and roentgenographic estimation of osseous age, when this was pertinent. Careful menstrual data were kept. Endometrial biopsies were done at the onset of all episodes of bleeding which terminated cycles studied by pregnanediol titers. Studies of vaginal smears or basal temperatures were not made.

ANALYSIS OF DATA

The clinical data comprising this study represent a fair sample of our total work; they embrace the results of quantitations of 2,193 twenty-four-hour specimens of 102 patients. These represent 30.8 per cent of all determinations done. The number of patients reported is equal to 43.7 per cent of those studied. The data excluded were those obtained upon patients in whom biopsies of the endometriums were lacking and during nongestational cycles in which various treatments were being administered; otherwise, no preferential selection of data for this study was made.

In the reporting and discussion of the data secured from our studies, we have used the simple term "pregnanediol" to mean sodium pregnanediol glucuronide. Our determinations are reported in terms of milligrams of sodium pregnanediol glucuronide, the compound actually extracted from the urine, rather than in terms of milligrams of actual pregnanediol. Venning and her group have reported their findings in terms of free pregnanediol.

A detailed summary of the pertinent data on the 102 patients studied follows:

A. 1. GYNECOLOGIC PATIENTS, WHO BLED FROM PROGESTATIONAL ENDOMETRIUMS AND WHO EXCRETED PREGNANEDIOL

1a. *Those Whose Bleeding Was Cyclic and Whose Endometriums Were Irregularly Proliferated.*—

Number of patients: 6.
Endometrial responses: M– (4 patients); M (1 patient); M+ (1 patient).
Total Pregnanediol (Preg., pregnanediol complex throughout remainder of data) determinations for group: 87.
Range of number of determinations per patient: 10 to 24.
Range of total amounts of Preg. recovered per patient: 16 to 93 mg.
Per patient average of total cyclic output of Preg.: 59.7 mg.
Range of times of first appearance of Preg.: 7th to 22nd day of cycle.
Range of times of disappearance of Preg.: 5th to 1st day prior to flowing.

1b. *Those Whose Bleeding Was Cyclic and Whose Endometriums Were Regularly Proliferated.*—

Number of patients: 15.

Endometrial responses: P– (5 patients); P (10 patients).
Total Preg. determinations for group: 232.
Range of number of determinations per patient: 8 to 32.
Range of total amounts of Preg. recovered per patient: 20 to 173 mg.
Per patient average of total cyclic output of Preg.: 49.4 mg.
Range of times of first appearance of Preg.: 6th to 25th day of cycle.
Range of times of disappearance of Preg.: 1st to 5th day prior to bleeding.

2a. *Those Whose Bleeding Was Excessive or Prolonged and Whose Endometriums Were Irregularly Proliferated.—*

Number of patients: 3.
Endometrial responses: M– (1 patient); M (2 patients).
Total Preg. determinations for group: 40.
Range of number of determinations per patient: 8 to 16.
Range of total amounts of Preg. recovered per patient: 8 to 135 mg.
Per patient average of total cyclic output of Preg.: 51.3 mg.
Range of times of first appearance of Preg.: 10th to 22nd day of cycle.
Range of times of disappearance of Preg.: 1st to 5th day prior to bleeding.

2b. *Those Whose Bleeding Was Excessive or Prolonged and Whose Endometriums Were Regularly Proliferated.—*

Number of patients: 4.
Endometrial responses: P– (2 patients); P (2 patients).
Total Preg. determinations for group: 73.
Range of number of determinations per patient: 12 to 25.
Range of total amounts of Preg. recovered per patient: 7 to 51 mg.

B. 1. GYNECOLOGIC PATIENTS, WHO BLED FROM ESTROGENIC ENDOMETRIUMS AND WHO EXCRETED PREGNANEDIOL

1. *Those Whose Bleeding Was Cyclic.—*

Number of patients: 7.
Total Preg. determinations for group: 133.
Range of number of determinations per patient: 14 to 25.
Range of total amounts of Preg. recovered per patient: 14 to 118 mg.
Per patient average of total cyclic output of Preg.: 50.4 mg.
Range of times of first appearance of Preg.: 5th to 29th day of cycle.
Range of times of disappearance of Preg.: 1st to 3rd day prior to bleeding.

2. *Those Whose Bleeding Was Excessive or Prolonged.—*

Number of patients: 3.
Total Preg. determinations for group: 49.
Range of number of determinations per patient: 15 to 17.
Range of total amounts of Preg. recovered per patient: 14 to 51 mg.
Per patient average of total cyclic output of Preg.: 38 mg.
Range of times of first appearance of Preg.: 13th to 27th day of cycle.
Range of times of disappearance of Preg.: 5th to 6th day prior to bleeding.
Per patient average of total cyclic output of Preg.: 25.2 mg.
Range of times of first appearance of Preg.: 15th to 24th day of cycle.
Range of times of disappearance of Preg.: 1st to 2nd day prior to bleeding.

A. 2. GYNECOLOGIC PATIENTS, WHO BLED FROM PROGESTATIONAL ENDOMETRIUMS AND WHO DID NOT EXCRETE PREGNANEDIOL

1a. *Those Whose Bleeding Was Cyclic and Whose Endometriums Were Irregularly Proliferated.*—

Number of patients: 5.
Endometrial responses: M– (1 patient); M (2 patients); M+ (2 patients).
Total Preg. determinations for group: 75.
Range of number of determinations per patient: 5 to 21.

1b. *Those Whose Bleeding Was Cyclic and Whose Endometriums Were Regularly Proliferated.*—

Number of patients: 15.
Endometrial responses: P– (7 patients); P (7 patients); P+ (1 patient).
Total Preg. determinations for group: 270.
Range of number of determinations per patient: 9 to 32.

2a. *Those Whose Bleeding Was Excessive or Prolonged and Whose Endometriums Were Irregularly Proliferated.*—

Number of patients: 1.
Endometrial response: M.
Total Preg. determinations: 5.

B. 2. GYNECOLOGIC PATIENTS, WHO BLED FROM ESTROGENIC ENDOMETRIUMS AND WHO DID NOT EXCRETE PREGNANEDIOL

1. *Those Whose Bleeding Was Cyclic.*—

Number of patients: 4.
Total Preg. determinations for group: 62.
Range of number of determinations per patient: 6 to 31.

2. *Those Whose Bleeding Was Excessive or Prolonged.*—

Number of patients: 2.
Total Preg. determinations for group: 37.
Range of number of determinations per patient: 14 and 23.

C. 1. GYNECOLOGIC PATIENTS, WHO DID NOT BLEED AND YET EXCRETED PREGNANEDIOL

1. *Those With Intercurrent Amenorrhea (No Bleeding for Six Months or Longer).*—

Number of patients: 3.
Endometrial responses: not studied.
Total Preg. determinations for group: 52.
Range of number of determinations per patient: 13 to 25.
Range of total amounts of Preg. recovered per patient: 19 to 59 mg.
Per patient average of total cyclic output of Preg.: 32.3 mg.

C. 2. GYNECOLOGIC PATIENTS, WHO DID NOT BLEED AND DID NOT EXCRETE PREGNANEDIOL

1. *Those With Delayed Menarche.*—

Number of patients: 7.
Total Preg. determinations for group: 169.
Range of determinations per patient: 7 to 46.

2. *Those With Intercurrent Amenorrhea (No Bleeding for Six Months or Longer).*—

Number of patients: 9.

Total Preg. determinations for group: 100.
Range of determinations per patient: 6 to 28.

3. *Those Past Menopause.*—
Number of patients: 6.
Total Preg. determinations for group: 86.
Range of determinations per patient: 4 to 26.

A. 1. OBSTETRIC PATIENTS, WHO WERE STUDIED AND TREATED BECAUSE OF THREATENING ABORTIONS AND WHO SUBSEQUENTLY ABORTED OR MISCARRIED

a. *Those Who Excreted Normal Levels of Pregnanediol.*—
Number of patients: 0.

b. *Those Who Excreted Initially and Continually Decreased Amounts of Preg.*—
Number of patients: 3.
Total Preg. determinations for group: 65.
Range of number of determinations per patient: 12 to 39.
Range of daily Preg. values: 0 to 18 mg.

Individual schematic protocols of these patients follow:

A. N., aged 24 years, para 5-5-0, abortion at 13th week: average daily Preg. values in mg. by weeks: x,x,x,x // x,x,x^{+},5* // 3,2,x,x // $^{\ddagger}_{**}$.

M. C., aged 23 years, para 1-1-0, abortion at 12th week: average daily Preg. values in mg. by weeks: x,x,x,x // x,x,x,x // x^{+},7*,8,0, $^{\ddagger}_{**}$.

G. B., aged 32 years, para 0-0-0, abortion at 13th week: average daily Preg. values in mg. by weeks: x,x,x,x // x^{+},x*,5,10 // 14,13,7,0 // 0, $^{\ddagger}_{**}$.

The symbols used in these protocols, and similar ones to follow have these significances: x, no Preg. determinations were done during the week so designated; numerals reported represent mg. of Preg. excreted daily (arranged by weeks); // indicates each interval of 4 weeks, dated from onset of last menstrual period; * and ** signify, respectively, the initiation and discontinuation of antiabortional therapy; $^{+}$ indicates onset of symptoms of threatening abortion; $^{++}$ indicates occurrence of abortion or miscarriage; antiabortional therapy embraced use of progesterone 1 to 10 mg. daily or every other day, together with use of estrogens and of chorionic gonadotropin (at times) during first 12-16 weeks.

A. 2. OBSTETRIC PATIENTS, WHO WERE STUDIED AND TREATED BECAUSE OF THREATENING ABORTIONS AND WHO SUBSEQUENTLY PROGRESSED TO TERM

a. *Those Who Excreted Normal Amounts of Preg.*—
Number of patients: 1.
Total Preg. determinations: 57.
Range of daily Preg. values: 0 to 20 mg.

Schematic protocol of this patient follows:

M. Mc., aged 25 years, para 0-0-0. Average daily Preg. values in mg. by weeks: x,1,2,11 // 15,10,14*,10 // 11,x,16^{+},20 // 6. R was continued to 36th week. Delivery 40th week.

b. *Those Who Excreted Decreased Amounts of Preg.*—
Number of patients: 0.

B. 1. OBSTETRIC PATIENTS, WHO WERE STUDIED AND TREATED BECAUSE OF HISTORIES OF RECURRENT ABORTIONS OR MISCARRIAGES AND WHO SUBSEQUENTLY ABORTED OR MISCARRIED

a. *Those Who Excreted Normal Amounts of Preg.*—

Number of patients: 1.
Total Preg. determinations: 80.
Range of daily Preg. values: 3 to 62 mg.

Schematic protocol of this patient follows:

R. M., aged 30 years, para 3-3-0, miscarried at 25th week. Average daily Preg. values in mg. by weeks: x,x,x,x // x,30*,20,11 // 10,20,22,21 // 26,29,32,38 // 50,57,x,x // x,x+,x,x // x, ⁂.

b. *Those Who Excreted Initially and Continually Decreased Amounts of Preg.*—

Number of patients: 1.
Total Preg. determinations: 102.
Range of daily Preg. values: 0 to 42 mg.

Schematic protocol of this patient follows:

E. W., aged 26 years, para 3-3-0, miscarriage at 29th week. Average daily Preg. values in mg. by weeks: x,x,0,0 // 4,0*,0,0 // x,x,14,12 // 24,21,15,23 // 34,31,27,28 // 26,x,x,x // x,x,x,x // x, ⁂.

c. *Those Who Excreted Essentially Normal Amounts of Preg. Until Immediately Prior to Abortion or Miscarriage.*—

Number of patients: 3.
Total Preg. determinations: 156.
Range of number of determinations per patient: 40 to 71.
Range of daily Preg. values: 0 to 80 mg.

Schematic protocols of these patients follow:

A. B., aged 35 years, para 10-10-0, miscarriage at 30th week. Average daily Preg. values in mg. by weeks: x,x,x,x // x,x,x,x* // x,x,x,x // x,x,x,x // x,x,x,x // x,31,32,31 // 44,45,46,53 // x+, ⁂. (Preg. daily values fell to zero during last week of determinations.)

L. R., aged 33 years, para 3-3-0, abortion at 17th week. Average daily Preg. values in mg. by weeks: x,x,3,14 // 23,18,25,14 // 19,12*,17,12 // 11,1,4,15+ // ⁂. (Daily Preg. values fell to zero during 2nd and 3rd weeks before abortion.)

S. P., aged 37 years, para 6-5-1, delivery of macerated fetus at 29th week. Average daily Preg. values in mg. by weeks: x,x,x,x // x,x,x,x // x,x,x,x // x,x,x,x* // 32,32,52,50 // 36,32,18,x // x,x,x+,x // ⁂. (Daily Preg. values fell to zero during last week of determinations.)

B. 2. OBSTETRIC PATIENTS, WHO WERE STUDIED AND TREATED BECAUSE OF HISTORIES OF RECURRENT ABORTIONS OR MISCARRIAGES AND WHO SUBSEQUENTLY PROGRESSED TO TERM OR ARE APPROACHING TERM

a. *Those Who Excreted Normal Amounts of Preg.*—

Number of patients: 3.
Total Preg. determinations: 263.
Range of number of determinations per patient: 42 to 154.
Range of daily Preg. values: 0 to 149 mg.

Schematic protocols of these patients follow:

A. H., aged 26 years, para 3-3-0, delivery at 40th week. Average daily Preg. values in mg. by weeks: x,x,x,x // x,x,x,x // x,x,23*,22 // 25,21,17,16 // 31,46,36,40 // 47,60,46,42 // 60,68,78,85 // 50,41,61,14 // 67,86,108**,x // x,x,x,x //.

E. M., aged 26 years, para 3-2-0, pregnancy now in 32nd week. Average daily Preg. values in mg. by weeks: x,x,x,x // x*,x,31,24 // 29,35,33,49 // 45,63,59,52 // R continued; determinations discontinued.

E. K., aged 33 years, para 5-4-1, pregnancy now in 34th week. Average daily Preg. values in mg. by weeks: x,x,x,x // x+,x*,x,21 // 24,10,x,14 // 28,26,30,30 // 34,33. R continued; determinations discontinued.

b. *Those Who Excreted Decreased Amounts of Preg.*—
Number of patients: 0.

DISCUSSION

The most striking and disconcerting data encountered in these studies are those upon the pregnanediol excretion of patients whose episodes of bleeding occurred from estrogenic and progestational endometriums. Our data, when they are analyzed, yield this information:

Of the 49 patients whose cycles terminated in progestational bleeding, 21, or 42.86 per cent, excreted no pregnanediol, and of the 16 patients whose cycles terminated in estrogenic bleeding, 10, or 62.5 per cent, excreted pregnanediol.

When the average total amounts of pregnanediol excreted by those individual patients having estrogenic and progestational bleeding are calculated, these are found to be of essentially the same order: those with estrogenic bleeding 46.7 mg., and those with progestational bleeding 48.4 mg.

These findings obviously indicate that no reasonable prediction as to the nature of the endometrial response at the end of an ovarian cycle may be made from data upon the urinary excretion of pregnanediol during that cycle.

The generally established reliability of studies of endometrial biopsies in identifying the presence or absence of normal corpus luteum activity is well known in clinical practice. Therefore, we accept the endometrial data as being faithful, and we are forced to reject the pregnanediol data as being unreliable.

The question arises as to whether the patients, who failed to excrete pregnanediol during progestational cycles, have some abnormality of ovarian function. We have been unable to identify any characteristic syndrome in these patients. We have good reason to believe these patients are of normal endocrine and gynecologic status: 3 of our patients were observed to become pregnant during cycles in which no pregnanediol was excreted; the pregnancies of 2 of these progressed to term while the other patient delivered a macerated fetus at the seventh month. Certainly endometrial data indicate that failure of pregnanediol

excretion is not associated with minimal progestational responses. The endometrial responses of the 21 patients in which these circumstances were present are summarized: M–, 1 patient; M, 3 patients; M+, 2 patients; P–, 7 patients; P, 7 patients; and P+, 1 patient.

In view of these facts, the assumption appears warranted that pregnanediol is not necessarily a major metabolic or excretionary product of the progestin secreted from corpora lutea of nongestational cycles.

No satisfactory explanation has been found for the excretion of pregnanediol by patients with estrogenic bleeding. It is highly unlikely that these patients were having normal ovarian cycles which were not mirrored by the endometriums, due, perhaps, to endometrial refractivity. Instances of this nature do occur but not with this frequency. Other findings upon these patients and their subsequent clinical courses are opposed to this theory. Refuge may be taken in the alternative that the material recovered from the urine by Venning's method might not have been sodium pregnanediol glucuronide. There are some good grounds for an assumption of this nature.

In addition to free pregnanediol and sodium pregnanediol glucuronide, Marker and his group[9] have found other members of the pregnane group in the urine of normal and pregnant women: pregnanol-3(α)-on-20, "epipregnanolon"; allo-pregnanediol-3 (α)-on-20, "epi-allo-pregnanlon"; allo-pregnanediol-3-(α)-20(α); and allo-pregnanediol-3(α)-20(α) The third one of these compounds has a melting point close to that of pregnanediol and as many as 7 mg. of it have been found in a liter of pregnancy urine. Westphal[10] calling attention to the preceding studies cautions that pregnanediol should not be regarded as the only compound with 21 carbon atoms which results from the reduction of progesterone. Qualitative studies of progestin metabolism may prove eventually to be far more productive and instructive than quantitative ones.

The inconsistencies between the times of first appearance of pregnanediol in the urine during ovarian cycles and its times of disappearance prior to bleeding lend little support to its correlation with the formation of progestin by the corpus luteum.

In view of the foregoing observations, there is little reason to anticipate the existence of significant relationships between the degree of progestational reaction of endometriums and the amount of pregnanediol excreted during associated cycles. These data confirm this lack of correlation: average total pregnanediol output of patients bleeding cyclicly from irregularly proliferated progestational endometriums, 59.7 mg.; of those bleeding cyclicly from regularly proliferated progestational endometriums, 49.5 mg.; of those bleeding excessively or prolongedly from irregularly proliferated progestational endometriums, 51.3 mg.; and of those bleeding excessively or prolongedly from regularly proliferated progestational endometriums, 25.2 mg.

The data upon patients who did not bleed are more consistent than those upon patients who experienced bleeding cycles. Only 3 of these 25 patients, 12 per cent, excreted pregnanediol. All of these 3 patients had had intercurrent amenorrhea for 6 months or longer. The range of the total amounts of pregnanediol excreted during periods of study comparable to those of patients having bleeding cycles was of essentially the same order as for the latter patients, i.e., 10 to 59 mg.

Additional facts upon the histories and subsequent courses of these patients may explain their excretion of pregnanediol upon the basis of the existence of cyclic ovarian function: 1 had diabetes mellitus; control of this was followed by return of cyclic bleeding. One had return of cyclic bleeding from oral steroid therapy and subsequently became pregnant. One, who had not bled in 3 years, had cyclic menstrual molimina. Unfortunately these observations were not controlled by studies of serial endometrial biopsies.

The fact that no pregnanediol was recovered from the urines of the 7 patients with delayed menarche and the 6 patients past the menopause may be significant. It may indicate that steroid-complexes of non-progestin origin and, therefore, not truly pregnanediol may have been recovered from the urines of the other patients with higher levels of ovarian function.

The data from studies upon the 12 obstetric patients are more consistent. All of these patients excreted some pregnanediol. Some definite but restricted correlations apparently exist between levels of urinary pregnanediol and the likelihood of abortion and miscarriage.

All of our patients whose pregnanediol values were initially and continually low subsequently aborted or miscarried despite intensive anti-abortional therapy which embraced the use of progesterone in daily doses as large as 10 mg. and combined frequently with the use of estrogens and chorionic gonadotropin.

Since in none of these patients were we able to improve the pregnanediol excretion by progestin therapy, knowledge of these low values was of no avail in arriving at correct therapeutic requirements. One of the sanguine hopes when the method first was described was that it would permit a practical application of this nature.

There was another group of patients, who, despite the excretion of normal amounts of pregnanediol during the early months of their pregnancies, ultimately aborted or miscarried. The normal pregnanediol excretionary curves of these patients during the early months of their pregnancies led to erroneous prognoses. (All were getting therapy). All of these patients, whose pregnanediol excretions were studied up until the terminations of their pregnancies, manifested, as a rule, marked decreases in these values during the week prior to abortion, some daily values always being zero. Since reports on these determinations are five days late when they come from the laboratory and since these falls in excretion

occurred despite intensive therapy, these delayed and revised prognostic data were of no practical or constructive import.

The converse to the foregoing observations has been found true: no patients who continually excreted normal amounts of pregnanediol aborted or miscarried.

Therefore, while these obstetric data warrant the assumption that pregnanediol, as measured by Venning's method, is likely a major and significant product of chorioplacental activity and metabolism, they do not delineate a practical application for the method in clinical obstetrics. It does little good to know that an abortion or miscarriage is imminent, if appropriate and effective therapeutic schedules cannot be put in force.

SUMMARY AND CONCLUSIONS

Results of a four-year study designed to evaluate Venning's pregnanediol method as a practical and trustworthy aid in the diagnosis of progestin levels in gynecologic and obstetric practice are reported. Data upon quantitations of 2,193 twenty-four-hour urines of 102 patients (90 gynecologic and 12 obstetric) are analyzed.

When correlations with studies of endometrial biopsies terminating ovarian cycles investigated by pregnanediol determinations were made, it was found that of 49 patients, whose episodes of bleeding occurred from progestational endometriums, 21, or 42.86 per cent, *excreted no pregnanediol* and that of 16 patients, whose episodes of bleeding occurred from estrogenic bleeding, 10, or 62.5 per cent, *excreted pregnanediol* in amounts of the same order as those excreting it in association with progestational bleeding. Some possible explanations of these variabilities are discussed.

More consistent data were secured on 25 patients who had no bleeding cycles. All of the 7 patients with delayed menarche and all of the 6 patients past menopause excreted no pregnanediol. Three of the 12 patients with intercurrent amenorrhea, however, excreted pregnanediol. The clinical records of these patients suggest the likelihood that these had cyclic ovarian functions.

No consistent relationships were identified between the curve of pregnanediol excretion and the predicated luteal phase of the cycle or between the degree of progestational proliferation of the endometrium and the amount of pregnanediol excreted.

The data upon the 12 obstetric patients were quite consistent. All excreted pregnanediol. The four patients, whose pregnancies progressed to term, despite either histories of recurrent abortions or intercurrent threats to abort, excreted normal amounts of pregnanediol. In 7 of the remaining 8, who aborted and miscarried, studies were continued sufficiently long to be significant. The pregnanediol excretions of these were either initially and continually low or became decreased with some

daily values dropping to zero seven to ten days prior to termination of pregnancy. Since these accidents to pregnancies occurred despite intensive progesterone therapy, these data on pregnanediol excretion were of no clinical value in gauging dosage levels.

The following conclusions are held warranted from the foregoing data: (1) Venning's method is unreliable as a diagnostic aid in gynecology; and (2) the data supplied by it in obstetrics at present permit no effective therapeutic endeavors, and while these may be of prognostic import, their belated warnings are often at variance with the prognosis suggested by earlier data.

These studies were supported from grants and fellowships available to us from the Research Council of Duke University, Ayerst, McKenna and Harrison Ltd., of Montreal, Canada, and Schering Corporation, Bloomfield, N. J.

Our group acknowledges the work done upon the studies reported in this communication by their past and present associates in the Endocrine Laboratory, including Catherine Ashley, Josephine Powers and Austin Salmon and that done by their former and present associates in the Endocrine Clinic: Drs. C. J. Pattee, G. J. Axelson, Norborne Powell, R. L. Pullen, J. A. Wilson, Violet Horner, C. D. Davis, J. H. M. Madden, and D. V. Hirst.

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CLINICAL EXPERIMENTS IN RELATION TO THE EXCRETION OF THE ESTROGENS*

I. Urinary Estrogens Before and After the Injection of Estrone Into a Patient With Surgical Menopause

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THIS and the following studies represent some of our efforts during the past two years to learn more about the metabolism of the sex steroids both in normal women, in those with functional disorders, and in those with pregnancy toxemia.

METHODS

The technique utilized for hydrochloric acid hydrolysis of urine, for extraction and separation of the estrogens, and for zinc-hydrochloric acid hydrolysis were the same as previously published.[1, 2]† Special precautions must be taken against loss or destruction of estradiol during semicarbazide treatment of the estrone-estradiol fraction. The whole procedure is carried out in a single receptacle. The evaporation after semicarbazone formation is performed in vacuo and alcohol is added immediately, since estradiol is rapidly destroyed in concentrated acid solution. Since the difference in estrogenic potency of this fraction before and after the semicarbazide procedure is the estrone value, any loss of estradiol would give a falsely high figure for estrone. Assay by difference is open to objection, especially when bio-assay must be used, but we have found this method more dependable, when small amounts of estrone are present, than Girard's separation and assay of the separated fractions.

Assays were performed upon mature-spayed rats of known reactivity to a standard dose of crystalline estradiol (0.1 γ in 0.1 c.c. of olive oil in one injection) and maintained in a primed condition by the induction of estrus (by test or a priming injection of estradiol) once in every seven to ten days. Each animal used for testing an unknown was in estrus five days previously. The material for a given assay was injected in three subcutaneous doses (0.1 to 0.2 c.c. of olive oil per injection) four hours apart and vaginal smears were taken forty-eight hours from the first injection. One rat unit (5 I. U. by our assay) was considered present in that dosage of the extract which produced positive smears in 4 of 6 rats or in 50 per cent of 8 or more rats, provided no more than 25 per cent of 8 or more rats showed positive smears at the next lower dosage. The difference between dosage levels introduced a range of values over which the end point might lie, amounting to 10 to 25 per

*This and the three papers on this subject to be published in succeeding issues were presented in brief before the New York Obstetrical Society on Jan. 13, 1942.

The Mrs. William Lowell Putnam Investigation of the Toxemias of Pregnancy aided by grants from the Committee on Research in Problems of Sex of the National Research Council.

†The references will accompany the fourth paper of this series.

cent of the end point figure recorded. Using this technique with our colony and with our criteria for interpreting smears, we have obtained practically uniform standardization values for the three crystalline estrogens in 12 assays of each that have been performed during the last three years. With 0.1 γ of crystalline estrone as the international unit, we find 1 I.U. in 0.1 γ of crystalline estriol and in 0.01 γ of crystalline estradiol.

In calculating the number of micrograms of estrogenic substance in urines, these standardization values are used, and it is assumed that all of the potency of each fraction is accountable to the specified estrogen. Although our present knowledge and the accuracy of the methods do not entirely justify this procedure, a much closer approximation of the amount of estrogen excreted results than if activity units alone are recorded. A considerable amount of investigation has convinced us that the methods of extraction and assay employed in these studies are as good as any available and sufficiently quantitative to yield results of physiologic significance.

The accuracy of all urine collections was checked by determination of creatinine.[3] Specimens were kept cold during the period of collection and extracted within twelve hours of the last voiding.

EXPLANATION OF TERMS

T_o symbolizes the total urinary estrogens excreted as such, that is, the total estrogenic potency of the urine after hydrochloric acid hydrolysis. It is the sum of the activities of the estradiol, estrone, and estriol fractions and is expressed in activity units (international units or estrone equivalents).

T_{zn}, also expressed in activity units, symbolizes the total estrogenic potency of the urine after prolonged hydrochloric acid hydrolysis in the presence of powdered zinc. This procedure has been shown[2] to convert any estrone in the urine into some compound approximately five times as active as estrone, to have no effect upon the potency of estradiol or estriol, and to render estrogenically active certain urinary constituents which are excreted in an inactive form and which are not rendered estrogenic by simple hydrochloric acid hydrolysis. "Unaccounted for" T_{zn} activity, therefore, is the difference between the total T_{zn} value and the sum of the potencies of the estradiol, estriol, and five times the estrone fractions.

EXPERIMENT

The subject, Miss M., aged 50 years, and in excellent health, had undergone supravaginal hysterectomy with bilateral salpingo-oophorectomy nearly eight years previously. She had taken estrogenic substances intermittently until one month before the inception of this study, the results of which are presented in Table I. Three days after the injection of estrone a series of severe hot flushes supervened.

The seventy-two-hour control specimen contained 90 I.U. of estrogenic activity, which was located in the estradiol fraction. Small amounts of estrogenic activity in menopausal urine have been reported before and assumed to come from the adrenal glands.

During the three days following the injection of 5 mg. of estrone, 3,350 I.U. were recovered, 64 per cent as estradiol, 19 per cent as estriol, and

TABLE I. MISS M. SURGICAL CASTRATE. URINARY ESTROGENS BEFORE AND AFTER INJECTION OF ESTRONE

		URINARY ESTROGENS AFTER HCl HYDROLYSIS				URINARY ESTROGENS AFTER ZN-HCl HYDROLYSIS			
		TOTAL (T_o)	ESTRADIOL	ESTRONE	ESTRIOL	TOTAL (T_{zn})	FROM T_o	UNACCOUNTED FOR	T_{zn}/T_o
72° control 2/3-6/41	I.U.	90	90 (100%)	0	0	135	90 (67%)	45 (33%)	1.5
	γ	0.9	0.9 (100%)	0	0				
2/10/41	5.0 mg. (5,000 γ or 50,000 I.U.) Estrone (Parke, Davis & Co. Theelin in oil) I.M.								
First 24° after inj. 2/10-11/41	I.U.	2,250	1,450 (65%)	475* (21%)	325 (14%)	4,350	4,150† (95%)	200 (5%)	1.9
	γ	94.5	14.5 (15%)	47.5 (50%)	32.5 (35%)				
48° 24-72° after inj. 2/11-13/41	I.U.	1,100	700 (64%)	100 (9%)	300 (27%)	5,800	1,500‡ (26%)	4,300 (74%)	5.3
	γ	47.0	7 (15%)	10 (21%)	30 (64%)				
Total 72° recovery after injection 2/10-13/41	I.U.	3,350 (6.7%)				10,150 (20.3%)		4,500 from	
	γ	141.5 (2.8%)	5,000 minus 141.5 = 4,860 γ or 48,600 I.U. lost estrone ←					↑	

*This value, obtained by difference in potency before and after semicarbazide treatment of the estrone-estradiol fraction, was confirmed by performing a separation with Girard's reagent.

†Zinc-hydrochloric acid hydrolysis of the ketonic fraction after Girard's separation (474 I.U. estrone) yielded 2,375 I.U., a fivefold increase in potency.[3] Therefore, of the total 4,350 I.U. after zinc-hydrochloric acid hydrolysis of the urine itself, 2,375 I.U. were derived from estrone and 1,775 I.U. from estradiol and estriol, neither of which is affected by zinc-hydrochloric acid hydrolysis.

‡Similarly, this value is the sum of 700 I.U. estradiol, 300 I.U. estriol, and 5×100 I.U. estrone.

17 per cent as estrone. In terms of activity, 6.7 per cent of the injected material found its way into the urine. This figure agrees with reported urinary recovery of injected estrone in dogs.[4, 5] In terms of weight, however, only 2.8 per cent of the injected estrone was recovered, 15 per cent as estradiol, 40 per cent as estrone, and 45 per cent as estriol. After zinc-hydrochloric acid hydrolysis, 10,150 I.U., 20.3 per cent of the injected material in terms of potency, were recovered. Fifty-six per cent (5,650 I.U.) of this total T_{zn} activity came from the estrogens present before zinc-hydrochloric acid hydrolysis, as explained in the footnotes of the table, leaving 4,500 I.U., or 44 per cent, unaccounted for.

DISCUSSION

If urine had been collected for another day following injection a little more estrogenic activity would probably have been recovered, but not enough to alter significantly the presented figures. From reports now appearing[4, 5] and our own as yet incomplete data, it is certain that some, less than 10 per cent, of the administered hormone was excreted in the bile and possibly through the intestinal mucosa.

We have repeatedly presented evidence[6-11] that estrone to estriol conversion is a gauge of progestin activity, but this subject following injection of estrone excreted a goodly amount of activity in the estriol fraction in the absence of any known endogenous progestin. However, we have also demonstrated that administered testosterone and adrenal cortical extract act like progesterone in inhibiting destruction and enhancing conversion of estradiol to estrone to estriol.[7, 10] Furthermore, we have found that pregnanediol glucuronidate, a physiologically inert excretion product of progesterone, augments the effect of progesterone upon estrogen metabolism, through protecting progesterone against destruction.[10] It begins to appear that retardation of steroid degradation may be the primary factor in the conversion mechanism. Thus, in the present experiment, the quantity of estrone administered may itself have clogged the estrogen destructive process enough to permit estrone to estriol conversion, or it may have had the same final effect indirectly through protecting adrenal steroids from destruction. That the high level of estrogen was either directly or indirectly preventing degradation is indicated by the difference in partition of urinary metabolites during the first twenty-four hours after injection, when total estrogens were high, and the last forty-eight hours, when the excretion per twenty-four-hour volume was one-fourth as great. In the second specimen, evidence for a marked increase in the rate of estrogen destruction is found in the drop in estrone and rise in T_{zn} to T_o ratio. The rate of estriol excretion decreased only 50 per cent during the last forty-eight hours, as compared with a 90 per cent drop in estrone, an observation which is in keeping with the known stability of estriol as compared with estrone to oxidative destruction.

The thesis that the partition of urinary estrogens provides an index of progestin activity, therefore, must be modified, especially when ovarian and placental secretions are absent or are not the predominating factors in steroid metabolism. In the nonpregnant female with active ovaries, however, and in pregnancy the thesis still holds, as demonstrated by the urinary findings after administration of progesterone (see second paper of this series), during the luteal phase of ovulatory cycles,[6, 11, and third paper of this series] and the parallel curves of estriol and pregnanediol in pregnancy.[8-10] Contrary to our previous assumptions,[6] based on the work of Pincus and Zahl,[12, 13] the uterus is not necessary for estrone-to-estriol conversion and the ovaries are not needed for the reversible estrone-to-estradiol reaction.

Acid hydrolysis of urine with the addition of powdered zinc has in our studies consistently given higher estrogenic activity than acid hydrolysis alone. We have shown that this procedure does not change the activity of estradiol or estriol but results in about a fivefold increase in the potency of estrone, ascribable to conversion of this ketone into estradiol, probably a mixture of the α and β forms.[2] The method, however, yields more estrogenic activity than can be accounted for even by maximum conversion of estrone, and this we have designated "unaccounted for." Although more complete hydrolysis with the longer boiling period of the zinc-hydrochloric acid procedure may contribute to this fraction, we have considerable evidence in favor of the assumption that resynthesis of estrogenic substance from inactive estrogen metabolites is the source of a large part of it, especially in urines with high T_{zn} to T_o ratios.[2] Certainly in the present experiment the 4,500 I.U. of "unaccounted for" activity must have come from the injected estrone and at that represents only about 9 per cent of the lost activity.

CONCLUSIONS

From this experiment we would conclude that in the castrate female: estrone is converted in the body both to estradiol and estriol; this conversion mechanism is favored by retardation of steroid degradation; the internal genitalia are not necessary for these processes; less than 3 per cent by weight of injected estrone reaches the urine in recognized forms; hydrolysis with the addition of zinc recovers more of the injected estrogen, a finding consistent with our hypothesis that a good part of the additional activity from zinc-hydrochloric acid hydrolysis represents rehydrogenation of inactive products of estrogen oxidation.

THE HISTOPATHOLOGIC DIAGNOSES OF THE ATYPICAL ENDOMETRIUM*

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IT IS the avowed purpose of far-seeing pathologists and clinicians to make their objective that stated by Virchow many years ago, namely "a functional interpretation of their pathologic findings." At present this is impossible in many instances, for example when the tissue studied represents an end stage of a process which has passed through many intermediate phases long lost to view, as in a kidney showing advanced chronic glomerulonephritis. In other instances as in the differential diagnosis of various varieties of appendicitis, the desirability or necessity of such a functional objective does not appear important. In recent years, however, in one field, namely in the diagnosis of the non-neoplastic endometrial states, the attempt to correlate functional status with histologic appearances has been consciously sought for and in some measure achieved. It is because of this attempted and moderately successful correlation between histologic character and functional status that the detailed study of the endometrium is of importance and certain inadequacies of diagnosis become apparent.

It is considered sufficient in general in making pathologic diagnoses to call attention to the dominant pathologic finding and neglect the remainder. In many cases of focally acute appendicitis and in many other nondiffuse pathologic states, as in patchy nephrosclerosis, the existence of normal areas are implied and understood though not explicitly stated and probably no great harm to understanding and practice result. But the requirements of diagnoses appear quite different in regard to the endometrium. In the appraisal of the pathologic status in perhaps no other tissue does a complete, detailed and co-ordinated survey appear so important as in the study of the endometrium. Too frequently the pathologist, habituated to specific diagnoses or to the clinicians' impatience with anything but such specific and final diagnoses, permits himself this indulgence though he often so does with misgivings and doubt. The facts are that the character of many endometriums does not permit specific all inclusive diagnoses and such diagnoses are in many instances misleading or, at best, inadequate. Sometimes in an effort to salvage the situation the term diplastic is used, in the hope that an amplication of the term will be asked for and its inadequacies rectified.

*Read at a meeting of the Obstetrical Society of Philadelphia, March 5, 1942.

For this undesirable situation there appears to be but two satisfactory solutions. The first and less satisfactory is to give as detailed a written description of the findings as possible in the hope that the description will be read. The second and the more satisfactory solution is to supplement this description with a personal study of the slide by the qualified clinician either alone or in collaboration with the pathologist. In this day of certification by Diplomate Boards, histologic knowledge is becoming an increasingly frequent acquisition by the gynecologist.

Even were the above-outlined objective achieved, the study of the endometrium by the pathologist and clinician in their attempt to arrive at a satisfactory opinion would suffer from a number of other possible limitations. Clinicians, more or less experienced, differ in the thoroughness with which they practice curettage and in the endometrial sites they are likely to explore. The same patient may yield different quantities and kinds of material in the hands of different gynecologists. Since as a result the tissue submitted may not be sufficiently variable and representative, and since the pathologist is to some extent dependent for his opinion upon the mere quantitative as well as qualitative aspects of the curettage, he may be misled. Thus focal hyperplasia may be present in an endometrium otherwise atrophic so that the pathologist observing hyperplastic areas would hesitate to make a diagnosis of unqualified hyperplasia when only a small amount of scrapings have been obtained at the curettage. Again, some clinicians do not record very precisely the amount of material they obtain, making the pathologist completely dependent for his quantitative estimate on the amount submitted for examination. This dependency too may fail the pathologist since it is the practice of some operators not to send all the scrapings they obtain to the laboratory but instead to select, often at random, portions for examination. This latter practice is undesirable since it substitutes a hurried, often capricious choice for the presumably unhurried and in some instances better qualified choice by the pathologist.

The considerations discussed above become important because of the lack of uniformity of the appearance of different portions of the endometrium under certain conditions. The proper status of the endometrium should be appraised on both quantitative and qualitative grounds. It is a matter of conjecture whether a hypoplastic but otherwise adequately secretory endometrium, is adequate for nidation. Should a small or moderately large focus of hyperplasia be accepted as the cause of bleeding in an otherwise normal endometrium, remembering of course that there is as yet no definitive opinion concerning the relationship between bleeding and hyperplasia? Does a relatively small focus of secretory endometrium in an otherwise hyperplastic tissue reflect the possibilities of successful nidation? Whatever the answers to these questions, the immediate clinical problem is certainly not advanced by merely listing an over-all diagnosis nor are we in this manner likely to

prepare material and facts for further clinical evaluation when our knowledge and insight increase.

Figs. 1 and 2 illustrate the variability of the histologic pattern in some endometriums.

Many studies have testified to our present inability to correlate clinical symptoms with tissue findings, though the latter is generally admitted to be as valuable as any single method of investigation at present available. Thus there have been observed the association of hyperplastic tissue with both amenorrhea and menorrhagia, and we and others have

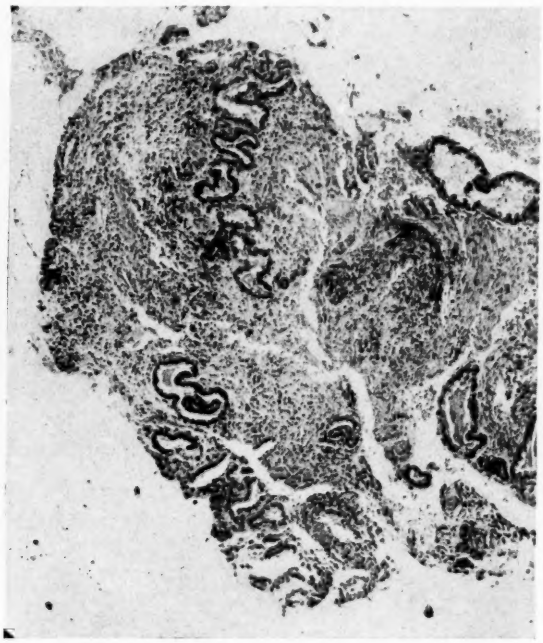

Fig. 1.—Patient, aged 32 years, had a prolonged menstrual bleeding. Area shows scarring and a few glands (×43).

observed secretory features in a generally hyperplastic tissue. Menorrhagia associated with secretory types of endometrium have been noted and particularly commented upon by Traut and Kuder.[1] Such findings, as these and others, cannot as yet be fitted into any consistent and simple physiologic or pathologic scheme except by some tortured interpretation or by assumptions which cannot at present be either substantiated or discredited.

In such a state of affairs it would appear more commendable to reveal rather than conceal our inadequacies by describing the findings and by not attempting unwarranted diagnoses. Because of such considerations one wonders whether the use of the biopsy technique may not be contributing in some measure to our present and future deficiencies in

knowledge. The biopsy technique has, of course, its legitimate applications, but those of us who have seen one small focus of decidua or adherent groups of chorionic villi, in an otherwise undistinguished endometrium or those of us who have been impressed with the variability of endometrial pattern in some endometriums, cannot but feel that frequently the study of only the small pieces obtained by this method, must in some degree be inadequate.

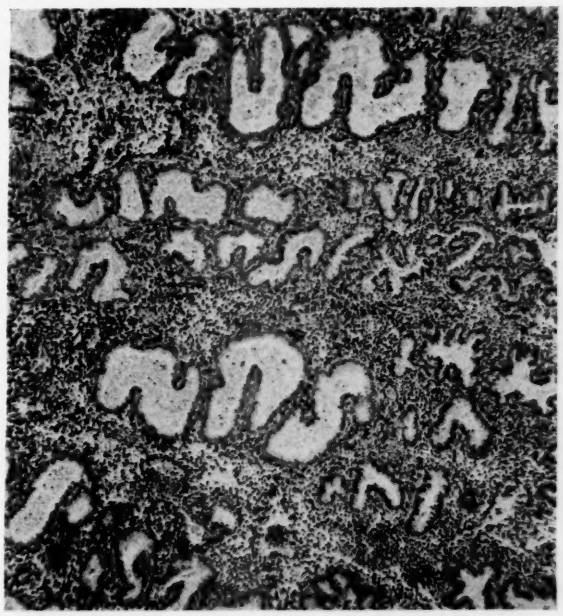

Fig. 2.—Same case as in Fig. 1, showing normal secretory endometrium (×65).

SUMMARY

Attention has been called to the variability of the histologic findings in different portions of curettings removed for various clinical conditions, and hence the necessity of utilizing as frequently as possible the procedure of curettage rather than that of biopsy.

Because of the present inadequate state of our knowledge and because of our inability to satisfactorily correlate many histopathologic findings with the hormonal status of the patient or with the inherent responsiveness of the endometrium, it is felt inadvisable in many instances to attempt all inclusive specific diagnoses. It is considered more advisable in these cases to restrict one's self to full descriptive reports supplemented by consultation and discussion between clinician and pathologist, in the hope that the future may bring clarification and unity to these objectively recorded findings.

REFERENCE

1. Traut, Herbert F., and Kuder, Alberta: Surg., Gynec. & Obst. 61: 145, 1935.

2019 PINE STREET

DISCUSSION

DR. F. SIDNEY DUNNE.—I believe the question of an endometrial biopsy is done with only one intention most of the time, namely to give the clinician or pathologist the information whether the patient is ovulating. It is well proved that endometrium ripens irregularly, so that you may have a rather confusing picture in interpreting a whole block of curettings. What is often taken to be premenstrual change is not a true endometrial change. It is classified as a pseudostratification or a gland cut on the diagonal which may be interpreted as premenstrual change. It is not unusual to find in a well-developed endometrium cystic glands which cannot be termed hyperplasia in the sense that the word is used. It does mean a definite clinical entity and you can have a well-developed hyperplasia.

I think the study of endometrium depends on the serial section, but we have no way of drawing conclusions to help the clinician as to where this pocket endometrial pattern has its clinical symptoms. You can have any type of endometrium which may give amenorrhea, menorrhagia, or oligomenorrhea. The thing we are getting at is interpretation of endometrial changes in the entire block, and try to interpret other areas which do not fit in with the menstrual history. We still have a lot to learn in interpreting endometrial patterns. It is not unusual to have normal endometrium falsely diagnosed as carcinoma or many other things, but the important thing is you may have a variety of histologic appearances in any group of endometrial curettings and turn back nothing to help the clinician.

We still have not reached the point where we can correlate endocrinology with our pathology.

USE OF SULFANILAMIDE POWDER IN GYNECOLOGIC AND OBSTETRIC OPERATIONS

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RECOGNITION of the principles governing the action of sulfanilamide led logically to its application directly to the tissues which need its effects most. Lockwood[11] enunciated these principles clearly when he stated that it works best when:

1. The supply of phagocytes is richest, such as in the peritoneum;
2. The greatest concentrations are in actual contact with the bacteria;
3. There is not much necrotic tissue present, with its protein digestion products which are capable of immobilizing the sulfanilamide molecules.

Therefore, the chief indications for the use of sulfanilamide powder in obstetric and gynecologic operations are:

1. Peritonitis, regardless of the causative organisms or the presence of gastric or intestinal contents;
2. Contamination of the peritoneal cavity at operation, either by opening this normally sterile cavity into continuity with a normally infected cavity, as for example, the vagina, or by trauma to, or removal of, infected tissues or organs such as pyosalpinges;

3. Prevention of formation of adhesions in cases where there is mechanical or chemical irritation or where there are large areas left unperitonealized after the removal of large tumors;
4. Abscess cavities which are opened and drained, such as a pelvic or Bartholin gland abscess.

The dosage depends upon the condition found at operation. The largest amount given is 15 Gm. in the peritoneal cavity plus four or five in the abdominal wall, but this amount is used only in severe cases of peritonitis where drainage is contemplated. Prophylaxis of peritonitis is accomplished by the use of 8 Gm. or less and it is questionable whether any should be put into the abdominal wound. The use of drainage calls for higher doses in order to allow for the escape of the powder in the drainage fluid. The presence of necrotic material and peritoneal exudates of caseous types also indicates the larger doses. The clean peritoneum absorbs the material more rapidly than the inflamed membrane, and very large doses are contraindicated in preventive applications, because toxic levels in the blood may be reached quickly.

The mode of application is not important, so long as the powder is kept dry and applied thinly and evenly. One good method is application by a sterilized insufflator, especially convenient in inaccessible places. The powder is prepared for use by heating it in tubes at 140° C. in a dry oven for two hours.

No serious local effects have resulted from the application of the powder in the doses given. The concentrations obtained in the peritoneum are found to be 75 to 100 times the blood level usually reached, and it is probably not all absorbed from the peritoneum for three days.

When a sulfa drug has been used by topical application, it is undesirable and usually unnecessary to supplement it by other methods of administration for three days afterward, and the use of oral medication of this type before operation in which it will be used intraperitoneally is inadvisable. These precautions will prevent a number of cases of chemical hepatitis, examples of which have been frequently noted, especially before these precautions were recognized as necessary. Cyanosis is frequent but less serious than hepatitis. Fever, which could be assigned to the use of the drug, and optic atrophy have also been reported after intraperitoneal application.

Our cases included complete hysterectomies, vaginal plastics, operations on tuboovarian abscesses, and miscellaneous clean cases, such as supravaginal hysterectomies and suspensions. In addition to these there were 23 miscellaneous infected cases with very serious conditions present before operation.

In the complete hysterectomies, the powder was divided between the upper end of the vagina and the cul-de-sac of Douglas. In cesarean sections, it was placed under the flap of peritoneum on the surface of

the uterus and in the lateral parts of the pelvis. In extraperitoneal types, it was put into the tissue spaces opened for the delivery of the child. It was used more often in cases of prolonged labor with ruptured membranes than in ordinary cases, the average elapsed time before section in the cases where sulfanilamide was used being twenty-seven hours' labor and thirty hours with ruptured membranes, while for the cases where sulfanilamide was not used, the figures were fourteen and seventeen hours, respectively. Elective sections are not included in these averages. Only four classical sections were done at the Woman's Hospital in the period covered by this study.

In vaginal plastic operations, the powder was put under the vaginal flaps, and into the peritoneum whenever the latter was opened. In tuboovarian abscesses, the powder was applied about the areas where the infection was thought most likely to have been spread. For comparison with these cases, similar types of operations from the work of the same year were taken. Although the comparison is not quite accurate, due to the tendency to use sulfanilamide in the more serious cases, and leave it out in the less serious, still it is of interest to note that some of the principles outlined above were as well borne out as could be expected in a series of this length. The mortality, the number, and the seriousness of the complications, the wound healing and the fever were used as criteria for evaluating the patients' toleration of the drug and the operative procedure. If the temperature rose to 100° F. or above at any time during the twenty-four hours, the day was counted as a day of fever. Temperatures were taken every four hours.

Among the cases of complete hysterectomy from the abdominal approach, 62 were done without sulfanilamide and 31 with sulfanilamide.

TABLE I. COMPLETE HYSTERECTOMIES

	IMPERFECT WOUNDS	COMPLICATIONS	DEATHS
Without sulfanilamide	4 (6.4%)	7 (11.3%)	3 (4.9%)
With sulfanilamide	3 (9.7%)	3 (9.7%)	1 (3.2%)

RESULTS

Three of the four imperfect wounds in the group without sulfanilamide were definitely infected, and the average duration of fever was nine days. In the group with sulfanilamide, none of the imperfect wounds were infected, the defects being due to fat necrosis and hematoma. In the cases where sulfanilamide was not used, the complications consisted of five urinary tract infections, one abscess of the vaginal vault, and one bronchopneumonia. Among the cases with sulfanilamide, there was one bronchopneumonia, one severe cyanosis due to sulfanilamide (this occurring in a 67-year-old hypertensive patient with nephrosclerosis), and one abscess of the vaginal vault following a complete hysterectomy done for myoma but complicated by abscesses in both tubes.

There were three deaths among those without sulfanilamide, one of which was due to carcinomatosis, and two to peritonitis. There was only one death among those treated with sulfanilamide and this was due to pulmonary embolism followed by coronary thrombosis. Thus, among the cases where no infection existed before operation, there was no death from peritonitis and no abscess of the vaginal vault, when sulfanilamide was used.

Only the major varieties of plastic repairs, such as cystocele, rectocele, and lacerated pelvic floor, or continence of urine, or fistula, were considered in this series. There were 28 cases of vaginal hysterectomy in which sulfanilamide was not used, and four developed abscesses of the vaginal vault. One of these patients died from this cause. Six patients who had vaginal hysterectomies and, in whom sulfanilamide was used, all escaped without abscesses.

TABLE II. VAGINAL PLASTICS

	IMPERFECT WOUNDS			COMPLICATIONS			DEATHS
	NO.	%	DAYS FEVER	NO.	%	DAYS FEVER	
Without sulfanilamide	12	8.3	9	35	24.4	8	1
With sulfanilamide	1	6.6	4	4	26.4	8	0

Five of the 12 wounds mentioned above were definitely infected, with an average of fourteen days' fever and evidence of poor healing, including the formation of abscesses, one of which, not included in this five, is the death reported above. Among the cases where sulfanilamide was used, there was only one infected wound and no deaths. The complications were largely urinary, consisting of cystitis and pyelitis, showing *Staphylococcus albus* or *Bacillus coli* on culture, but there was also one case of bronchopneumonia and one of endometritis following a curettage and plastic operation. All the complications were urinary among the cases with sulfanilamide. A total of 143 plastics was done without sulfanilamide and 15 with it.

As previously noted there was a marked tendency to use sulfanilamide in the cases considered potentially infected. There were 111 cases in which sulfanilamide was not used and 34 in which it was used.

TABLE III. CESAREAN SECTIONS

	IMPERFECT WOUNDS			COMPLICATIONS			DEATHS
	NO.	%	DAYS FEVER	NO.	%	DAYS FEVER	
Without sulfanilamide	3	2.7	8	10	9.9	8	0
With sulfanilamide	1	3.0	24	2	6.0	15	0

Of really infected wounds, there were two among those without sulfanilamide and one among those with sulfanilamide. The complications were mild respiratory, urinary, breast, and parametrial infections. The patient with the infected wound, in whom sulfanilamide had been used, also developed paralytic ileus, pleurisy, and thrombophlebitis. Her operation was done after she had been in labor for thirty-seven hours. The other complication was a respiratory infection.

TABLE IV. TUBOOVARIAN ABSCESS

	IMPERFECT WOUNDS			COMPLICATIONS			DEATHS
	NO.	%	DAYS FEVER	NO.	%	DAYS FEVER	
Without sulfanilamide	1	10.0	9	0			0
With sulfanilamide	2	15.3	8	0			1

Ten cases were done without sulfanilamide and 15 with sulfanilamide. The death occurred in a woman with large bilateral tuboovarian abscesses, myomas, and peritonitis. A dose of 8 Gm. was put into the peritoneal cavity, followed by 6 doses of 1 Gm. each every four hours by mouth. On the second postoperative day, the blood level was 30 mg. The oral medication was stopped, and in forty-eight hours the level fell to 10 mg.; however, she died on the fifth postoperative day.

There were 27 patients without evidence of infection and in whom no infected cavity was opened into continuity with the peritoneum, in which sulfanilamide was used. One of these had thrombophlebitis and left lower lobe embolism, but recovered. Another whose hospital course had been normal, died at home of pulmonary embolism on the fortieth day after operation.

There remain 23 cases of miscellaneous infections in which sulfanilamide was used, bringing the total for all cases in the year to 143. The most interesting was that of a white woman of 76 years with no discernible heart or kidney lesions, but emaciated and in only fair general condition, who was admitted because of lower abdominal pain and a mass. A barium enema study showed diverticuli of the colon, but incidentally did not show gallstones. At operation, the liver felt normal, but the gall bladder was three times normal size and felt tense. No stones were palpable. The uterus contained several large myomas, and the scheduled hysterectomy was done. The patient went into shock and was given 100 c.c. of gum acacia-glucose solution intravenously. Six grams of sulfanilamide was put into the abdominal cavity. She developed increasing jaundice and fever (107° F.) and died twenty-four hours after operation. No additional sulfa medication had been given at any time.

A woman with strangulated inguinal hernia and gangrene of the intestine died after an operation in which 8 Gm. was used. Four patients with carcinoma and involvement of the bowel by the tumor or by radiation effect, all died within a few days of operation from pneumonia and peritonitis. Sulfanilamide was used successfully in three mastectomies. It was also used in six cases of appendicitis, but all those whose peritoneal culture showed the presence of bacteria in the peritoneal fluid at the time of operation, had infected wounds in spite of the sulfanilamide.

A middle-aged white woman had peritonitis of unknown origin, which involved the entire cavity equally with a thick, fibrinous exudate. The appendix was removed in the belief that it was the focus of infection, and 8 Gm. were put into the cavity and distributed equally. She developed and recovered from a bilateral lobar pneumonia, being given therapeutic doses of sulfathiazole by mouth after the second postoperative day. She had only five days of fever.

One case of pyometra showing gram-positive cocci had an infected wound following puncture of an atrophic uterus by the tenaculum. An-

other patient had a foreign body removed from the abdominal cavity several days after a section. Four grams were placed in the peritoneum at the second operation, with an uneventful convalescence. A woman with a carcinoma of the fundus and postradiation adhesions had 4 Gm. placed in the abdominal cavity. The stay sutures became infected and she had a peritonitis with twenty-nine days of fever, but recovered.

A patient admitted with a postoperative vesicovaginal fistula, had one ureter implanted into the bowel, and sulfanilamide was used. She died of pulmonary embolism on the twentieth day.

A 240-pound woman with chronic gall bladder disease had a cholecystectomy and appendectomy, followed by evisceration on the fifth day. No sulfanilamide had been used at this operation, but when the wound was resutured, 16 Gm. were used. She died forty-eight hours later. Fourteen grams of powder were placed in the wounds of a combined abdominoperineal resection of the colon for radiation stricture. The patient recovered after forty-eight days of fever.

SUMMARY

1. A brief review of principles gleaned from the literature is presented.

2. All the cases in which sulfanilamide powder was used at operation at the Woman's Hospital during 1941 are reviewed, and only two complications due to the use of the drug were noted. One was a severe cyanosis, and the other was hepatitis, which ended in death of patient, but other factors than the sulfanilamide were operating in this case, and only 6 Gm. were used.

3. Prevention of abscesses at the upper end of the vagina and prevention of peritonitis are the two clear-cut objectives to be striven for in the use of the powder in complete abdominal and in vaginal hysterectomies. In our short series, progress was made toward both of these. In cases with infection, prevention of peritonitis is more difficult to evaluate, and abscess formation harder to control, due to the variability in degree and virulence of infection and amount of spill.

4. Sulfanilamide did not prevent urinary, respiratory, nor circulatory complications, nor did it rescue moribund patients. Its use cannot obviate the need for good judgment and early treatment.

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ORIGIN OF ENDOMETRIOSIS FROM THE MESENCHYME OF THE CELOMIC WALLS

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THE controversy about the origin of endometriosis has divided the investigators into two groups, one advocating a local origin and the other suggesting transportation of material from the endometrium. Stimulated by the rise of our knowledge of latent developmental potencies, several adherents to the former idea undertook to explain ectopic endometriosis by activation of latent potencies in cells embryologically related to the endometrium. Similarly, the present work is concerned with the application of the author's recent embryologic results to the theory of endometriosis. It should be understood that the following discussion has the sole purpose of pointing out how the origin of endometriosis in all known locations can be explained on the basis of our present embryologic knowledge. This will oppose theories of transportation of tissue cells from the endometrium only so far as they are based on the assumption that in certain locations endometriosis cannot develop from local cells. In line with this aim, only the problem of possible local origin of endometriosis will be considered in the following pages.

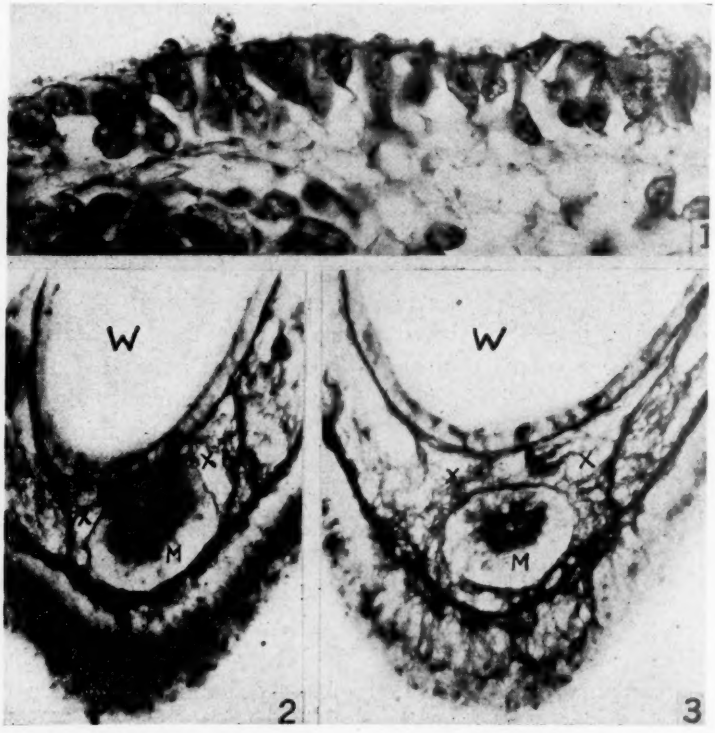
No detailed survey of the literature will be given, since there are numerous reviews of this subject on hand. Many investigators assume that part or all of the epithelium of the serous cavities, being the mother tissue of the Müllerian ducts, may give rise to dystopic endometrial epithelium. This theory was then extended, mainly by Heim,[1] to include the mesenchyme of the caudal parts of the celomic walls. This assumption was based on the fact that in the early embryo mesenchymal cells originate from the future peritoneal epithelium. However, part of Heim's considerations are embryologically ill-founded. He designates the mesenchyme of the cloacal portion of the former celomic cavity* as a possible source of endometriosis, holding that the female genital organs develop in that area. In fact, the urogenital ridges originally reach into the thoracic region where the Müllerian ducts first appear. When finally cases of endometriosis in the extremities were found, Biebl[2] suggested that all mesenchyme of the body might have the potencies necessary for the formation of endometrial epithelium.

*Author's free translation of "Mesenchym im Bereich des Kloakenabschnittes der früheren Cölomhöhle" (Heim:[1] p. 303).

In considering the embryologic basis of the endometriosis problem, we must first review certain aspects of the development of the celomic wall from which the Müllerian ducts eventually will originate. As has long been known, the celomic wall of early embryos does not consist of well-defined epithelium and connective tissue. The cells of the layer lining the celomic cavity have protoplasmic processes on their basal side, which are interwoven and structurally identical with those of the underlying mesenchymal cells (Fig. 1). Furthermore, many daughter cells of this superficial layer sink deeper into the tissue and become part of the mesenchyme. Thus, the celomic wall of the early embryo must be considered as one unit, comprising both the superficial and deep layers. Later, in human embryos during the fourth and fifth week, the superficial layer assumes all structural characteristics of a typical epithelium. However, as shown in a recent review,[3] this epithelium is still capable of cooperating with the adjacent mesenchyme in forming one common unit in which the two tissues cannot be distinguished. This happens particularly during early stages of organ formation from the celomic wall, such as in the initial phases of gonad and adrenal development. The fact that the limb buds develop from the celomic wall in a similar manner, will be discussed and evaluated below. The celomic lining may form mesenchyme long after its transformation into an epithelium. This happens particularly in the peritoneum, covering the Müllerian ducts, the so-called tubal ridge.[3] The readiness of the cells of the celomic wall to change from epithelial to mesenchymal arrangement, or vice versa, is also manifest in the organs developing from this tissue. This comprises the Müllerian ducts in addition to the gonads and adrenal cortex. These ducts, although originating as distinctly epithelial primordia from an epithelial portion of the celomic lining, give rise to typical embryonic connective tissue. This occurs to a considerable extent in chick and cat embryos where Müllerian cells near the caudal end of the growing duct change their properties and become part of the mesenchyme surrounding the duct itself[3] (Figs. 2 and 3). A similar condition was also found in human embryos, although probably not as extensively as in the chick.[4] It can thus be concluded that at least part of the nonepithelial tissues of the uterus are derived along with the epithelium from cells of the Müllerian ducts.

According to these considerations, the resultant tissues must be regarded as possible bearers of the potencies of endometrium formation. Nonepithelial cells of the uterine wall itself are closest related to the endometrial epithelium since part of them are derived from the Müllerian ducts at comparatively late embryonic stages, long after these ducts have acquired characteristic shape and differentiation. These cells must therefore be regarded as the possible source of those endometrioses of the uterus which are not continuous with the epithelium of the normal endometrium. In the second place we have to consider the mother tissue

of the Müllerian ducts, namely, the celomic walls. This includes not only the epithelium of the serous membranes, but also the underlying connective tissue and the organs formed by these tissues in the embryo. No definite boundaries of the connective tissue of the celomic walls against that of other origin (somites, etc.) can be given. As indicated above, we have no reason to restrict the area of possible endometrial



Figs. 1 to 3.—Mesenchyme formation from the lining of the colomic cavity and from the Müllerian duct (after Gruenwald[3]).

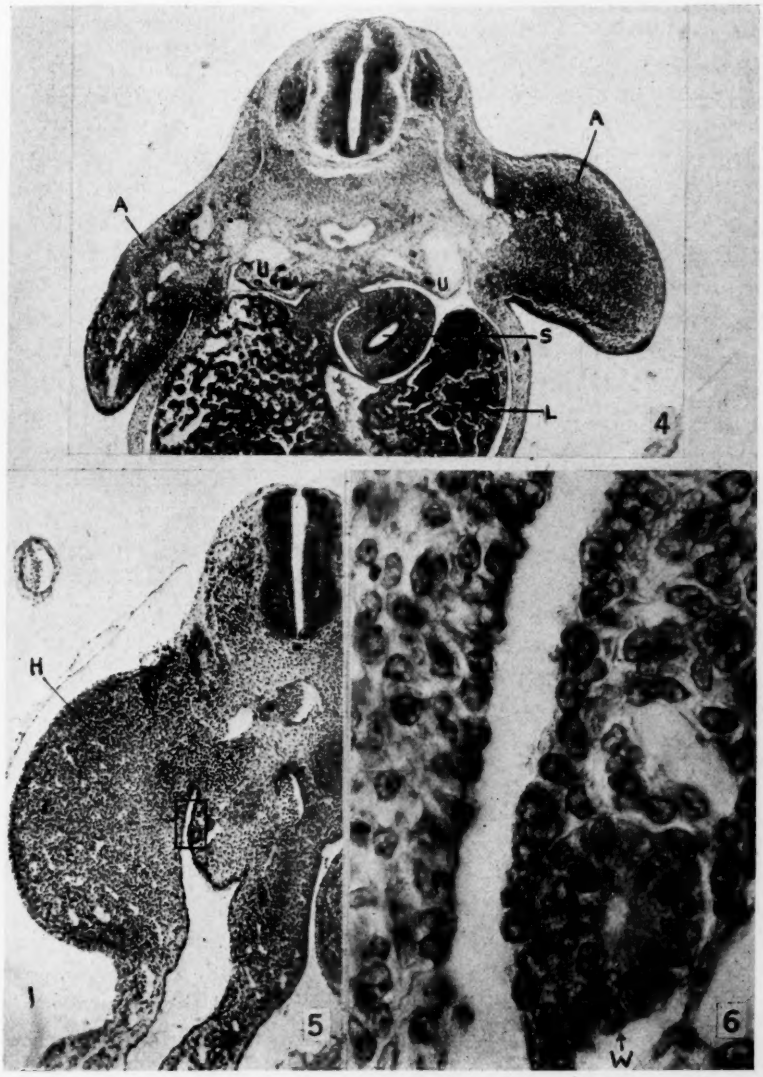
Fig. 1.—Celomic wall of a human embryo of the third week. Hemalum—eosin stain. No epithelium is present. The cells of the superficial layer are on their basal side structurally identical with the underlying mesenchyme and some of their daughter cells become part of it.

Figs. 2 and 3.—Müllerian duct and surrounding tissues of a chick embryo of six days and three hours. Gomori's silver impregnation. Fig. 3 shows the beginning subdivision of the Müllerian primordium into the duct proper (*M*) and a tissue between it and the Wolffian duct (*W*) in which argyrophil fibers indicate the beginning transformation into mesenchyme (*X*). A more cranial section of the same duct (Fig. 3) shows this process in a farther advanced stage. The basal membrane of the original Müllerian primordium is dissolving (left side of figure), and the newly formed mesenchyme between the Wolffian and Müllerian ducts is now characterized by a typical argyrophil framework (*X*).

potencies to the lower portion of the peritoneal cavity. At the time when the primordia of the Müllerian ducts first appear, the urogenital ridges reach cranially to the level of the upper thoracic segments.

The possibility of origin of endometriosis from these tissues of the celomic walls accounts not only for the common locations of that anomaly, but also for one whose explanation appeared extremely difficult to previous investigators. This is endometriosis of the extremities.

It has long been known that the mesenchyme of the limb buds develops from the parietal mesoderm. Bardeen[5] describes this as follows: "In part it may come from the primitive body segments, but it seems probable that in the main it comes from the parietal layer of the unsegmented mesoblast." This parietal mesoderm is part of the celomic wall,



Figs. 4 to 6.—The close topographic relation of limb buds and urogenital ridges is illustrated by cross sections of the arm region of a 5 mm. human embryo (hematoxylin-eosin stain*) (Fig. 4), and the hind leg region of a 6.5 mm. rat embryo (azan stain) (Fig. 5). Fig. 6 is a high-power view of the area marked in Fig. 5. The celomic lining adjoining the leg primordium (left side of figure) is still in its primitive condition comparable to Fig. 1, and can thus contribute to the tissue of the limb. *A*, Arm bud; *H*, hind leg primordium; *L*, liver; *S*, stomach; *U*, urogenital ridge; and *W*, Wolffian duct.

*From the Embryological Collection of the Department of Anatomy, University of Illinois, Chicago. I am indebted to Dr. O. F. Kampmeier for his permission to use this specimen.

and Filatow[6] describes early limb bud development in amphibians as occurring in a similar manner as briefly mentioned above in reference to early stages of gonad and adrenal development. Study of human and mammalian embryos reveals that here, too, the limb buds form from the parietal mesoderm at a time when the celomic lining (the later epithelium and mother tissue of the Müllerian ducts) still participates in the production of cells of that tissue. It can thus be seen that the mesenchyme of the limb bud is in its development closely related to the mother tissue of the uterine epithelium, both originating from the celomic wall. Figs. 4 to 6 may serve to illustrate the close relations of limb buds and urogenital ridges in early embryos. Fig. 4, taken from a cross section of a 5 mm. human embryo, shows the arm buds attached to the celomic wall in closest proximity of the cranial portion of the urogenital ridges, at a level very near the future site of the primordia of the Müllerian ducts. In Fig. 5, a similar picture is presented from the hind leg level of a 6.5 mm. rat embryo. Higher magnification (Fig. 6) reveals that even at this relatively late stage the celomic lining at the site of the leg primordium has not differentiated into an epithelium and may therefore still contribute to the tissue of the leg. We can thus include the extremities in our considerations concerned with the celomic walls. It is unnecessary to assume that all mesenchyme of the body may produce endometriosis, as was suggested by Biebl.[2]

In view of these close relations of limb primordia and urogenital ridges, one might almost wonder why we do not find many more cases of endometriosis of the extremities. However, we must remember that specialization of tissues proceeds during development, and the farther away an embryologically related tissue is in space or differentiation from the normal primordium, the less likely it will form germs resembling that primordium.

SUMMARY

Embryologic considerations show that endometriosis in all known locations may originate from the local tissues. The celomic walls, including epithelium and connective tissue, are in their development related to the Müllerian ducts and must therefore be regarded as possible bearers of the developmental potencies of endometrium formation. This also includes various structures arising from the celomic walls, among them the gonads and the extremities. The nonepithelial tissues of the uterus itself are in particular, closely related to the uterine epithelium, since part of their cells are given off by that epithelium (the Müllerian ducts) during embryonic life.

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THE USE AND POTENCY OF SYNTHETIC ESTROGENS*

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NOTWITHSTANDING the vast and ever-increasing literature on endocrinology, I am less enthusiastic now about the value of general endocrine therapy in gynecology than I was a few years ago. However, this does not apply to the estrogens. Today there is a more widespread use of the estrogens than formerly, and this appears to be warranted. The estrogens have a large field of usefulness in gynecology and a limited applicability in obstetrics. All investigators agree that estrogens readily suppress undesired lactation. These hormones are occasionally of benefit for the induction of labor, particularly in cases of missed labor, if used in very large doses and especially if combined with posterior pituitary extract. Likewise, the estrogens are sometimes helpful in cases of uterine atony during labor. White and Hunt[1] have found the estrogens most helpful in the treatment of diabetes in pregnancy and Van S. Smith and Smith[2] observed encouraging results with estrogens (combined with progesterone) in the toxemias of pregnancy.

In gynecology the prime indication for the use of estrogens is to overcome the distressing symptoms of the menopause. However, these hormones are also of distinct benefit in cases of gonorrheal vulvovaginitis, vaginal hypoplasia, senile vaginitis, menometrorrhagia and some cases of dysmenorrhea. The estrogens have also been used to overcome other abnormal conditions such as amenorrhea, hypoplasia of the uterus, and underdevelopment of the breasts, but in my opinion changes following such therapy are only temporary. The estrogens may be administered by mouth, sublingually, by hypodermic, by vagina, by rectum, by local application in an ointment, and by subcutaneous implantation in the form of crystals or pellets. For most indications, the subcutaneous route yields the best results but for some conditions such as gonorrheal vulvovaginitis and senile vaginitis, the local application of the hormone is preferable. Where prolonged action is desired, the subcutaneous implantation of pellets and crystals of estrogen is most helpful. However, because of the hesitancy of most physicians to resort to subcutaneous implantation, my associate Dr. S. C. Freed and I utilized the principle of implantation of crystalline estrogens in a form which does not sacrifice the convenience or practicability of simple injections. We utilized a suspension of estrone crystals in an aqueous medium on the assumption that, after injection into the tissues, the aqueous medium is rapidly

*Read at a meeting of the Obstetrical Society of Boston, February 17, 1942.

absorbed, leaving a deposit of crystals in the tissues to be absorbed slowly just as with implants. Laboratory experiments revealed that the estrus induced in castrate rodents with such a preparation persisted for a much longer time than with similar quantities of estrone in oil solution or even estrone suspended in oil.

We tested the therapeutic efficiency of aqueous suspension in a series of 44 menopausal patients. As a control we used 21 menopausal women to whom were given the same doses of estrone but suspended in oil instead of in water. The aqueous suspension in estrone proved to be superior to the oil suspension. In addition to the enhanced therapeutic efficiency, another advantage in using aqueous suspensions of estrone over oil solutions, is the freedom from possible sensitivity reaction to the oil.

All the patients received 5 mg. of estrone once a week for three weeks and some of them experienced relief for ten or more weeks after the last injection of aqueous estrone. It is doubtful that the estrone crystals were retained in the tissues for this length of time. It is more likely, as Salmon, Geist and Walter[4] have postulated for estrogen implants, that the slow uniform absorption of the estrogens allows for a physiologic readjustment to estrogen deprivation amounting at times to an actual curing of the patient.

SYNTHETIC ESTROGENS

In 1938 Dodds and his associates[5] synthesized diethylstilbestrol which possesses the properties of the natural estrogens. Stilbestrol is the mother substance from which diethylstilbestrol is derived. Stilbestrol has little estrogenic activity, whereas diethylstilbestrol (generally referred to as stilbestrol in the literature) has great estrogenic effect. The advantages of the synthetic estrogens are the great effectiveness of oral administration and their low cost. A disadvantage is that a fairly large proportion of the women who take diethylstilbestrol, experience disagreeable symptoms, chiefly nausea, vomiting, epigastric pain, headache, and dizziness. Generally the larger the dose taken the greater the likelihood of distress, because in most cases reducing the dosage eliminates the aftereffects. Thus far it has not been proved in human beings that diethylstilbestrol produces damage to any organs even when huge doses are administered. Notwithstanding the absence of proved injury, attempts have been made to synthesize estrogens which will be just as effective as diethylstilbestrol but will produce fewer disturbances. During the last few years, Dr. Freed and I have investigated not only diethylstilbestrol, but also hexestrol and a product known as 118-B.*

In most instances the claims for the relative therapeutic effectiveness of estrogens have been based on their activity as determined in laboratory animals, principally the rat and mouse. The assumption that data

*The diethylstilbestrol and the hexestrol were supplied by the Abbott Laboratories and the 118-B was prepared by Schieffelin & Co.

so obtained can be accepted for the human being has resulted in considerable confusion in the standardization of estrogen therapy. In the first place, results obtained from assays differ widely, as indicated by the fact that the rat unit of estrone as determined in different laboratories, varies as much as several thousand per cent when compared to a weighed amount of crystalline material. The same applies for assays in the mouse. In a compilation of data on the subject, Freed[6] illustrated the inconsistencies in animal assays and came to the conclusion that any statement regarding the relative therapeutic activity of estrogens on the basis of animal assays is liable to considerable error. For this reason I believe that at present the only satisfactory test object for the therapeutic efficiency of the estrogens is the human being.

There are a number of ways of assaying the activity of estrogens in the human being. Some investigators utilize the changes in the vaginal mucosa of menopausal women following estrogen administration as an index of estrogen activity, in a manner similar to that of the castrate rodent. There are objections to this index. In the first place, it requires considerable experience to read properly and interpret vaginal smears, and second, the reading is subject to much experimental error. Furthermore, since we know that untreated menopausal women have varying degrees of proliferation of the vaginal mucosa, this cannot be an entirely satisfactory means of assay. Still further, there is no evidence that the vaginal mucosa of a group of menopausal women will respond to a definite amount of estrogen with the same degree of uniformity.

An attempt has been made to use the endometrium as a means of assaying estrogens administered during the menopause. This procedure is distinctly more cumbersome than the use of vaginal smears and is open to even more criticism than the latter. Untreated menopausal women by no means uniformly present an atrophic endometrium. Many show not only endometrial proliferation but actual hyperplasia. Hence, endometrial changes cannot be used as criteria for estrogen activity.

In our investigation we have selected as the end point in the assay of estrogens in human beings, the subjective response of menopausal patients. It is acknowledged that the evaluation of such a response may be obscured by numerous uncontrolled factors. Nevertheless, this method has been selected for the assay for a number of reasons, not the least of which is the fact that the chief purpose in administering estrogens is to relieve the menopausal patient of her subjective symptoms. Such an assay requires no special technique and a large number of patients may be included in a study with little difficulty. In order to eliminate as many distracting factors as possible from this study, we established certain criteria. Only those patients were selected who complained of moderate or severe menopausal symptoms. Those who had complaints which were of doubtful origin or possibly might be confused with psychic changes due to environmental or social complications, were not included in the group tested. The patients treated were limited to those having

at least two distinct hot flushes daily together with other symptoms commonly found in the menopause, such as nervousness, irritability, and emotional instability. The psychic factors associated with any form of therapy involving subjective sensations were reduced to a minimum by eliminating any therapeutic suggestions, such as a promise of beneficial results or leading questions concerning the therapeutic responses. In addition, the subjective changes of all the patients were evaluated by us alone in as constant a manner as possible, thus eliminating differences in interpretation of results which are prone to develop where a number of clinicians are treating the same group of patients. Furthermore, the estrogens were administered in several dose levels in the manner which is used for assaying estrogens in laboratory animals. Following are the data of three synthetic estrogens, diethylstilbestrol, hexestrol and 118-B, assayed in this manner.

METHODS AND RESULTS

The procedure carried out in the experiments was as follows: At various intervals, patients were given different levels of one of the three synthetic estrogens for oral use. For example, some women were given 1 mg., 2.5 mg., and 5 mg. daily of hexestrol, others received 0.5 mg. and 1 mg. of diethylstilbestrol and still others were given 1 mg., 2.5 mg., and 5 mg. of 118-B. Therapy was usually started by administering the highest level of the estrogen. After three weeks of treatment, the therapeutic response was evaluated and recorded in the following terms: "negative," "slight," "good," and "excellent." In the evaluation of the therapeutic response, the disappearance of the hot flushes was used as the most important criterion of relief. The other menopausal symptoms, such as nervousness, perspiration, irritability, etc., were also considered in this evaluation. After the first period of treatment, the dosage was dropped to the next lower level and maintained in this manner for three or more weeks. After the patient's response to the new dosage was evaluated, the dose in the case of hexestrol and 118-B was dropped to the third level and this was maintained for at least three weeks after which another evaluation was made. Following this, the type of estrogen administered was changed. Some women did not complete the entire course of assays due to refusal, because of unpleasant symptoms which arose, lack of cooperation, and other reasons. However, 82 women were given all three synthetic estrogens, 118 women were given diethylstilbestrol and hexestrol, and 44 women were given only the three different doses of hexestrol. With the use of the technique we employed, there is no need for control with either untreated patients or patients who receive placebos, inasmuch as each dosage level controls the next. The psychic factor of administering some form of medication is thus reduced.

Tables I to III show the therapeutic results of the assays of the three synthetic estrogens and also the incidence of unpleasant symptoms.

THERAPEUTIC RESPONSE OF MENOPAUSAL PATIENTS FOLLOWING ORAL ADMINISTRATION OF DIETHYLSTILBESTROL, HEXESTROL AND 118-B

Table I indicates that of the 53 women who took 0.5 mg. diethylstilbestrol daily, 9 derived no benefit, 17 had slight improvement, 18 were

TABLE I. DIETHYLSTILBESTROL

0.5 MG. DAILY			1 MG. DAILY		
NO. OF PATIENTS	RESULT	TOXIC REACTION	NO. OF PATIENTS	RESULT	TOXIC REACTION
9	Negative		5	Negative	
17	Slight		10	Slight	
18	Good		27	Good	
9	Excellent		23	Excellent	
53		5 9.4%	65		18 27.7%

satisfactorily relieved and 9 had complete relief from all symptoms. In this group of 53 women, 5 (9.4 per cent) experienced unpleasant reactions, such as nausea, headache, and dizziness. Of the 65 women who took 1 mg. diethylstilbestrol daily, 5 derived no benefit, 10 had slight improvement, 27 were satisfactorily relieved and 23 had complete relief. In this group of 65 women, however, 18 (27.7 per cent) experienced unpleasant symptoms. This agrees with the almost universal opinion that the larger the dose of diethylstilbestrol taken, the greater the frequency of disagreeable symptoms.

TABLE II. HEXESTROL

1 MG. DAILY			2.5 MG. DAILY			5 MG. DAILY		
NO. OF PATIENTS	RESULT	TOXIC REACTION	NO. OF PATIENTS	RESULT	TOXIC REACTION	NO. OF PATIENTS	RESULT	TOXIC REACTION
21	Negative		7	Negative		15	Negative	
10	Slight		13	Slight		5	Slight	
6	Good		29	Good		22	Good	
			11	Excellent		23	Excellent	
37		0	60		2 3.3%	65		9 14%

Table II shows that of the 37 women who took 1 mg. hexestrol daily, 21 derived no benefit, 10 had slight improvement, and 6 were satisfactorily relieved. No patients in this group experienced unpleasant symptoms. Of the 60 women who took 2.5 mg. hexestrol daily, 7 derived no benefit, 13 had slight improvement, 29 were satisfactorily relieved, and 11 had complete relief. In this group of 60 women, 2 (3.3 per cent) experienced unpleasant symptoms. Of the 65 women who took 5 mg. hexestrol daily, 15 derived no benefit, 5 had slight improvement, 22 were satisfactorily relieved and 23 had complete relief. Of these 65 women, 9 (14 per cent) experienced disagreeable side effects. As with diethylstilbestrol, the larger dose produced a greatly increased incidence of nausea, headaches, and dizziness.

Table III shows that of the 25 women who took 1 mg. of 118-B daily, 2 derived no benefit, 5 had slight improvement, 14 were satisfactorily relieved, and 4 were completely relieved. None of these 25 women experienced unpleasant reactions. Of the 39 women who took 2 mg. of 118-B daily, 5 derived no benefit, 9 had slight improvement, 16 were satisfactorily relieved, and 9 had complete relief. Only 1 of these 39 women (2.6 per cent) had nausea and dizziness. Of the 18 women who took 5 mg. of 118-B daily, 3 derived no benefit, 1 had slight improve-

TABLE III. 118-B

1 MG. DAILY			2 MG. DAILY			5 MG. DAILY		
NO. OF PATIENTS	RESULT	TOXIC REACTION	NO. OF PATIENTS	RESULT	TOXIC REACTION	NO. OF PATIENTS	RESULT	TOXIC REACTION
2	Negative		5	Negative		3	Negative	
5	Slight		9	Slight		1	Slight	
14	Good		16	Good		7	Good	
4	Excellent		9	Excellent		7	Excellent	
25		0	39		1 2.6%	18		2 11.1%

ment, 7 were satisfactorily relieved, and 7 had complete relief. Of these 18 women, 2 (11.1 per cent) experienced disagreeable symptoms.

It will be noted that a larger number of patients failed to respond to 5 mg. hexestrol than to 2.5 mg. of this substance. This apparent paradox is due to the fact that the women were first given the largest doses. Those who failed to respond at all were not given the 2.5 mg. dose. The 7 women who failed to respond to the 2.5 mg. dose had received benefit from the 5 mg. dose.

It is apparent from the data in the tables that a satisfactory daily therapeutic dose of diethylstilbestrol is 1 mg., of hexestrol 2.5 to 5 mg., and of 118-B, 1 to 2 mg. The minimal effective doses are 0.5 mg. diethylstilbestrol, 2.5 mg. hexestrol, and 1 mg. 118-B.

Of 46 women questioned concerning the relative merits of diethylstilbestrol and hexestrol the response was as follows:

28 found 2.5 mg. hexestrol daily equal to 0.5 mg. diethylstilbestrol
14 found 2.5 mg. hexestrol daily better than 0.5 mg. diethylstilbestrol
4 found 2.5 mg. hexestrol daily less effective than 0.5 mg. diethylstilbestrol

Likewise, among 48 women the following observations were made:

34 found 5 mg. hexestrol daily equal to 1 mg. diethylstilbestrol
6 found 5 mg. hexestrol daily better than 1 mg. diethystilbestrol
8 found 5 mg. hexestrol daily less effective than 1 mg. diethylstilbestrol

The incidence of toxic manifestations which is associated with the ingestion of the synthetic estrogens is an important matter, particularly because apparently this is the only drawback to the use of these estrogens. The tables indicate that the larger the dose of these estrogens, the greater the incidence of toxicity. Hexestrol is significantly less toxic than diethylstilbestrol, although the incidence of disagreeable symptoms from hexestrol is appreciable. Likewise, 118-B is definitely less toxic than either of the other two, and it is probably no more toxic than the natural estrogens. However, more data are necessary before this point can be determined definitely.

The results of this study are at variance with those of Bishop and his associates.[7] These investigators reported that hexestrol and diethylstilbestrol are of equal potency, but our study shows that hexestrol is only about one-fifth as effective as diethylstilbestrol. Furthermore, Bishop maintains that hexestrol is relatively free of untoward reactions. While we have found that hexestrol is definitely less toxic than diethylstilbestrol, it is by no means free from unpleasant sequelae.

SUMMARY

Three synthetic estrogens, diethylstilbestrol, hexestrol, and 118-B were tested for their therapeutic efficiency by assay in humans. The subjective response of menopausal patients was used as the end point in this assay. The usual uncontrolled factors encountered in such a study were largely eliminated by using multiple dosage levels of the estrogens as well as other precautions. The results indicate that all three synthetic estrogens are highly effective in relieving the distressing symptoms of the menopause if proper dosages are used. A satisfactory daily therapeutic dose of diethylstilbestrol is 1 mg., of hexestrol, 2.5 to 5 mg., and of 118-B, 1 to 2 mg. The larger the dose of synthetic estrogen used, the greater the likelihood of untoward reactions. Hexestrol is definitely less toxic than diethylstilbestrol, and 118-B is far less toxic than either diethylstilbestrol or hexestrol.

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URINARY INFECTION IN PREGNANCY DUE TO FLEXNER DYSENTERIAE

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SHIGELLA paradysenteriae (flexneri) seldom has been described as the causative organism in pyelitis and/or cystitis of pregnancy. For this reason four cases are reported, with four others described in the literature. The communication emphasizes that urinary infections of this nature have usually not been preceded by clinical evidence of gastrointestinal disease, and that confusion may arise in proving the identity of the Flexner organism bacteriologically.

CASE REPORTS

CASE 1.—(38-1879.) A 23-year-old para ii was admitted April 10, 1940, in the eighth lunar month of pregnancy, with a history of chilliness, fever, and costovertebral angle tenderness for several days. The

family and past history were irrelevant. Examination revealed an eight months' gestation. Clumps of pus cells were found in the urine. The day after admission pain developed in both lumbar areas associated with chills and fever of 100.4° F. The pyrexia and discomfort continued intermittently for twelve days. Urine cultures grew Flexner dysenteriae on seven different occasions between April 12 and June 17. During the same interval, six stool cultures were negative for the same organisms.

After administering 18 Gm. of sulfanilacetylimid within three and one-half days, April 14 to 17, there was no further temperature elevation. However, the urine cultures remained positive for bacilli Flexner. On June 1, 1940, the patient delivered a normal, mature, female infant who was found to have Flexner dysenteriae in the urine after the first week of life. On Nov. 7, 1940, and Sept. 10, 1941, urine cultures from the mother showed no pathogenic organisms. The baby was not reexamined, but according to the mother there were no gastrointestinal or urinary disturbances during the first fifteen months of life.

CASE 2.—(38-14983.) A white, 32-year-old, para ii was admitted April 25, 1940, in labor at term. The past and family history were not unusual except that the patient had acquired syphilis in 1927. Subsequently adequate antisyphilitic therapy was given. The catheterized urine showed a trace of albumin and many clumps of pus cells.

After a five-hour labor, a normal, female child, weighing 2,705 Gm., was born. On the seventh post-partum day, the mother developed a one-day fever with a temperature of 101.4° F., and with urinary frequency and dysuria. The urine revealed pus and cultures were positive for Flexner dysenteriae. Symptoms disappeared after two days' bed rest and administration of four liters of fluids daily. The mother left the hospital on the ninth post-partum day before further studies could be made.

CASE 3.—(40-5700.) A 27-year-old, white, para i, was admitted April 25, 1940. The past and family history were normal. About March 25, two months after the last menstrual period, the patient began to have severe shaking chills, pain in both flanks radiating to the costovertebral angles, urinary frequency, dysuria, and cloudy urine. These symptoms were associated with hyperemesis gravidarum. The uterus, the size of a four months' gestation, was larger than the history would indicate. There was fever of 101.5° F. The white count was 6600, hemoglobin 11 Gm. (Haden-Hausser), and blood agglutination tests for Malta fever, typhoid, paratyphoid A and B, Rocky Mountain spotted fever, tularemia, and dysentery were negative. The urine contained 22 pus cells per high power field with one-plus albumin, but no sugar or blood. Cultures of the urine grew Flexner bacilli. Intravenous and retrograde pyelograms were normal except for mild right hydronephrosis.

Treatment consisted in administration of 3,500 c.c. of fluids daily and bed rest. Within four days, the symptoms disappeared and the patient went home. Approximately one month later the family physician reported that the patient had a recrudescence of the urinary infection and made the statement that the gastrointestinal tract was free of infection. Symptoms were alleviated by giving neoprontosil, grain xl, daily for one week. The antepartum and puerperal course then continued uneventfully.

CASE 4.—(42-2405.) A 14-year-old primigravida was admitted March 10, 1942. The uterus was the size of a thirty weeks' gestation, and catheterized urine specimens repeatedly showed many clumps of pus. Cultures were positive for Flexner bacilli. The ante-partum course remained normal even though no specific therapy was instituted. Record of the post-partum course was not available.

BACTERIOLOGY

Shigella paradysenteriae (Bacterium flexneri) was isolated in pure culture from the urine of four patients. There were 19 urine and 10 stool examinations. The urine samples were inoculated into dextrose meat infusion broth and on eosin-methylene-blue and blood agar plates; the latter were placed under 10 per cent carbon dioxide. Nonlactose fermenting colonies were transferred to Russell's double sugar agar slants, which were later used to inoculate dextrose, mannite, maltose, lactose, xylose, and sucrose fermentation tubes. Tryptophane broth was also inoculated and likewise agar slants, the latter for the purpose of obtaining agglutinogen.

The stool specimens were cultured in selenite F enriched broth and on desoxycholate and eosin-methylene-blue plates. If, after twenty-four hours, nonlactose fermentors were not found on the plates, new plates were inoculated from the selenite broth. Nonlactose fermenting colonies were treated as described previously.

The organisms in each case were gram-negative, indole producing, nonmotile rods that fermented dextrose, mannite, maltose, and xylose, but failed to ferment lactose and sucrose. The lactose fermentation tubes were held two weeks before being discarded as negative.

In all cases the identification was confirmed by agglutination tests. Twenty-four-hour cultures on meat infusion agar slants were suspended in 0.9 per cent saline and routine agglutination tests made. The isolated organisms were then set up against the following antisera: polyvalent dysentery, Flexner, Hiss, and Sonne dysentery, typhoid, and paratyphoid A and B. Agglutination titers are recorded in Table II. Agglutination studies using the patient's serum against isolated strains of *Shigella paradysenteriae* were not done.

DISCUSSION

Perusal of the literature disclosed four additional cases of urinary infection in pregnancy due to bacillary dysentery, Flexner. Between Jan. 1, 1939, and March 1, 1942, there have been four cases among 5,504 obstetric admissions to this Hospital, or an incidence among urinary infections of 1 to 18.

Table I shows that 7 of the 8 patients had their initial symptoms antepartum and one post partum. Clinically 2 had pyelonephritis, 2 cystitis, and 4 pyelitis. Recrudescences occurred in 2 patients. In one instance the pregnancy was interrupted because there was no response to ureteral catheterization (Stewart, 1938). Treatment in the other seven cases included sulfonamides, 3; antivaccine, 1; bacteriophage, 1; and no

TABLE I. DATA ON EIGHT RECORDED CASES OF URINARY TRACT INFECTION IN PREGNANCY DUE TO FLEXNER DYSENTERIAE

AUTHOR	NO. OF CASES	AGE OF PATIENT	DURATION OF PREGNANCY IN MONTHS	URINE CULTURE (FLEXNER)	STOOL CULTURE	BLOOD AGGLUTINATION FOR DYSENTERY	CLASSICAL DIAGNOSIS	THERAPY
Calalb and Jonesco[1]	1	? Primigravida	8	Positive	One positive	Negative	Pyelonephritis	Given antivaccine for six days
Cheatham[2]	1	25	7	Positive*	Positive	Positive 1/640	Pyelonephritis	Bacteriophage introduced into kidney pelvis and intramuscularly
Stewart[5]	1	20	2 (recurrent attacks)	Positive	Positive	Positive 1/640	Pyelitis	Ureteral catheterization and interruption
Van Ravenswaay[6]	1	27	5	Positive*	Positive	Negative	Pyelitis	Mandelic acid and sulfanilamide
Diddle and McKee	1	27	4 (recurrent attacks)	Positive (with few *B. coli* once)	Negative	Negative	Pyelitis	Neoprontosil
	1	23	9	Positive	Positive once (contaminated with urine)	Negative	Pyelitis	Sulfanilacetylmid
	1	32	Seventh postpartum day	Positive* (Baby also had positive)	Negative (Baby's stool negative)	Not done	Cystitis	No specific therapy
	1	14	7.5	Positive	Negative	Not done	Cystitis	No specific therapy

*Reported negative three weeks to three months later.

specific measures except increasing the fluid intake, 2. Five women had bacteriologic evidence of gastrointestinal infection. However, two of the five had only one positive stool culture. It was known that the specimen of one patient had been contaminated with urine.

Seven other cases of urinary infection in nonpregnant females and males (Forester, 1918; Neter, 1937) were gathered from the literature. The authors have seen three others (one baby, one woman, one man). Seven of the 10 were girls, 1 a nonpregnant woman, and 2, men. The girls had pyuria, either with or without symptoms of cystitis or pyelitis, while the woman contracted pyelonephritis during the course of a gastrointestinal infection, and the men had pyelitis.

The preponderance of this type of infection in females would suggest that ascending infection through the bladder is more easily acquired, probably because the urethral orifice is not as well shielded anatomically as in males.

TABLE II. RESULTS OF AGGLUTINATION TITERS FOR POLYVALENT DYSENTERY AND FLEXNER DYSENTERIAE ANTISERA

CASE	SPECIMEN	NUMBER OF SPECIMENS	POLYVALENT DYSENTERY ANTISERUM*	FLEXNER ANTISERUM†	REMARKS
38-1879	Urine	7	1:80	1:160	Urine cultures negative five months later
	Stool	6	No dysentery organisms isolated		
Newborn baby of 38-1879	Urine	3	1:320	1:640	No later cultures or agglutinin studies
	Stool	2	No dysentery organisms isolated		
38-14983	Urine	2	1:160	1:320	Subsequent studies not done
40-5700	Urine	3	Positive, but titer not recorded	Positive, but titer not recorded	Recrudescence of infection in pregnancy
	Stool	1	No dysentery organisms isolated	No dysentery organisms isolated	
42-2405	Urine	4	1:320	1:640	Pyuria
	Stool	1	No dysentery organisms isolated	No dysentery organisms isolated	

*An original titer of 1:4,000 against homologous strain.
†An original titer of 1:1,280 against homologous strain.

From the bacteriologist's point of view one must be prepared to find dysentery organisms in locations other than the gastrointestinal tract. *Shigella paradysenteriae* (flexneri) were found in this institution from a cutaneous abscess (1) and a cervix (1). In each case stool and urine cultures were negative and no agglutinins were demonstrable. Also, there was no other pathologic process from which the organism might have invaded the infected area. In addition to the cultural and serologic studies described, the patient's blood should be tested for agglutination against known strains of dysentery organisms. In early cases, however,

a high titer is not to be anticipated and there may be a complete absence of demonstrable agglutinins. Checking the organism against antisera for typhoid, paratyphoid A and B helps to eliminate the possibility of an atypical typhoid or paratyphoid organism. Holding the lactose medium for two weeks aids in ruling out the paracolon group which at times may mimic typhoid, paratyphoid, or dysentery organisms. It is probable that urinary tract infection in pregnancy due to the Flexner organism is not as rare as the literature suggests, but failure to ascertain its presence is due either to confusing it with the paracolon group or to inadequate bacteriologic study.

SUMMARY AND CONCLUSIONS

Analysis of 8 cases of urinary tract infection in pregnancy due to *Shigella paradysenteriae (Bacterium flexneri)* revealed that the clinical symptoms produced might be severe or of only minor importance. Since treatment varied considerably, no comment on therapy is warranted, except to say that this type of infection seemed to respond to the usual measures employed for cystitis or pyelitis. An incidence of one in 18 obstetric urinary tract infections attributed to the Flexner organism suggests that this type of infection is more common than formerly believed.

Previous history of gastrointestinal disease was usually not obtained. The organism may be confused with the paracolon group. Differentiation and identification require thorough cultural and serologic study.

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Eagle, Harry, and Hogan, Ralph B.: The Intravenous Drip and Other Intensive Methods for the Treatment of Early Syphilis, Science **95:** 360, 1942.

The authors used over 2,000 syphilitic rabbits, treated with mapharsen, on the following twelve experimental schedules:

Intravenous drip (5 to 6 hours daily) for 1, 2, and 4 days.
Multiple injections each day for 1, 2, and 4 days.
Single daily injections for 1, 4, and 12 days.
Injections every other day (3 times weekly) for 4 and 8 weeks.
Weekly injections for 6 weeks.

They arrive at the conclusion that the margin of safety and the amplitude of tolerated dose over minimum curative dose could be increased by prolongation of treatment. Furthermore, the authors are of the opinion that their assumptions can be applied to human beings. A safe compromise can be worked out between the unduly prolonged eighteen-month schedule, and the dangerous 5-day program. Twelve clinics are now submitting these results to clinical trial.

L. M. Hellman.

PRIMARY PERITONEAL PREGNANCY

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IN THE vast majority of instances, extrauterine pregnancy results from the nidation of a fertilized ovum in some portion of the mucosal lining of the Fallopian tube. The selection of this point of nidation appears to rest on a delay of eight to nine days in the transit of such an ovum to the uterine cavity.[1, 2] The factors producing delay may be obvious, as in chronic salpingitis, or obscure. Much more rarely ectopic gestation results from a failure of the ruptured Graffian follicle to expel the mature ovum. Subsequent fertilization within the follicular space gives rise to one of the two forms of primary ovarian pregnancy.[3] The present knowledge of the active part played by the tube in securing the freshly expelled ovum,[4, 5] together with the fact that about eight to nine days elapse before the fertilized ovum becomes capable of nidation,[1, 2] explains quite obviously why primary extrauterine pregnancies are found most commonly in these two locations. These factors would seem to play a much greater part than the hypothesis which has been put forward that nidation can take place only in Müllerian tissue.[6]

Should the ovum be expelled from the follicle, become fertilized, and develop over a period of eight to nine days[1, 2] without being captured by the fimbriated extremity of the tube, it seems most likely to the author that nidation will take place in any tissue, regardless of its origin, with which the blastocyst is in contact. With the exception of the germinal epithelium of the ovary, such tissue must be either visceral or parietal peritoneum. Such a pregnancy must be termed a primary peritoneal pregnancy.

The criteria upon which the proof of such a pregnancy must rest are: (1) that both tubes and ovaries are normal with no evidence of recent or remote injury, (2) the absence of any evidence of a uteroperitoneal fistula, and (3) the presence of a pregnancy related exclusively to the peritoneal surface and young enough to eliminate the possibility of secondary implantation following a primary nidation in the tube. Some authorities[7-9] state that primary abdominal pregnancies are rare, while others,[10, 11] most recently Novak,[12] deny the possibility of this type of extrauterine gestation.

In reviewing some of the more widely quoted instances in the literature, the first case reported appears to be that of Gallabin[13] (1896). His patient showed a ten weeks' ovum in the cul-de-sac. She died from

hemorrhage after its removal. The nidation site and the pelvic organs were subjected to careful examination following autopsy. A committee of the London Obstetrical Society studied the findings, and, while admitting the possibility that the site of the pregnancy might have resulted from secondary implantation after early extrusion of the ovum from a primary fimbrial nidation, came to the conclusion that the case represented a true primary peritoneal pregnancy. Wittauer[14] (1903) next reported a patient, in whom the tubes and ovaries were found to be normal, the omentum containing a small blood clot in which chorionic villi were found. These findings might also have been produced by the early extrusion of a fimbrial tubal pregnancy with secondary implantation in the omentum. Hirst and Knipe[15] (1908) report what appears to be an undoubted instance, the ovum being about six weeks of age and implanted in the back of the left broad ligament above and to the outer side of the uterosacral ligament. The posterior leaf of the broad ligament formed the reflexa covering the maternal blood space. The tubes and ovaries appeared normal. Hammacher[16] (1910) reported an instance in which it was thought that the ovum was implanted on the external peritoneal aspect of the right tube. Maxwell, Eastman and Smetana[17] (1927) reported a similar case in which the ovum was thought to be implanted on the external surface of an apparently completely occluded left tube. In both the latter instances, while the microscopic sections seem convincing, the very location of the pregnancy gives rise to some doubt as to whether the ovum did not enter through the tubal mucosa.

These cases by no means represent a complete survey of the literature but illustrate the manner in which the possibility of true peritoneal implantation may be questioned. The case reported by Hirst and Knipe[15] (1908) appears to be least open to doubt. Because the following case appears to lend strength to the possibility that primary peritoneal nidation may take place, it was thought to be worthy of report.

CASE REPORT

Mrs. S. I., aged 27 years, para i, gravida ii, was admitted on Oct. 14, 1940, to the Gynecological Service, Bellevue Hospital, with a chief complaint of pain in the lower abdomen, radiating upward to the chest. This had begun suddenly at noon of the same day following violent sexual intercourse. Nausea and vomiting had occurred five times since the onset of pain. Her last menses had occurred on Sept. 14, 1940, and her following period was about two weeks overdue.

General examination showed a young woman who appeared in mild shock. Her blood pressure was 82/68, pulse, weak with a rate of 114, and temperature, 97° F. General physical examination revealed the following positive findings. The abdomen showed moderate soft distention with generalized tenderness. No rigidity was present. Pelvic examination showed the cervix to be posterior, closed, and firm. It was normal in appearance and showed no discharge. The corpus uteri was anterior, not enlarged, and nothing abnormal could be made out in either adnexal region except for moderate tenderness. The white blood count showed 13,300 with 83 per cent polymorphonuclear leucocytes. The hemoglobin was found to be 92 per cent (Dare). Urine examination showed negative findings.

Because of the history, the diagnosis of an internal injury, possibly involving the bladder, was entertained, but, by the following morning, increasing evidence of intraperitoneal hemorrhage was present. A laparotomy was performed with a preoperative diagnosis of extrauterine pregnancy. On opening the abdomen through a lower abdominal midline incision, the peritoneal cavity was found to be filled with fluid and clotted blood. Both tubes, ovaries, and broad ligaments appeared to be perfectly normal. The uterus was in normal position, not enlarged. On the posterior aspect, about 1½ cm. medial to the insertion of the left tube was a small round slightly elevated bluish area about 7 to 8 mm. in diameter. In the center of this was a small ragged opening about 1 mm. in diameter from which active bleeding was taking place (Fig. 1). The left horn of the uterus containing the entire involved area was removed, the uterine wound being closed by sutures. The remainder of

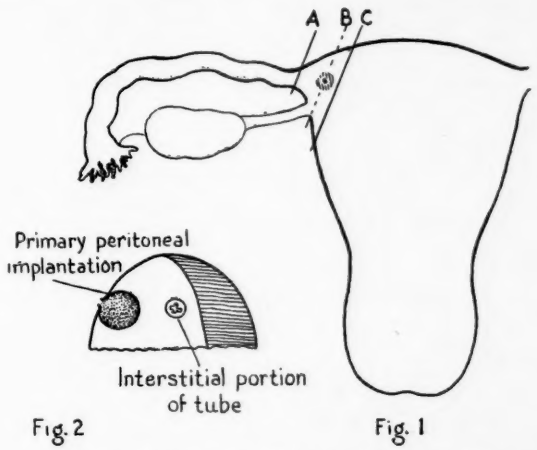

Fig. 1.—Diagram showing location of nidation site. Area between lines *A* and *C* excised at operation.

Fig. 2.—Diagram of cross section taken through line *B*, Fig. 1, showing relation of maternal blood space to peritoneum and to interstitial portion of tube. Shaded area of anterior myometrium discarded from material subjected to microscopic examination.

the left tube, the left uteroovarian ligament, and the upper part of the broad ligament were utilized to cover the uterine closure. It is to be regretted that the left tube and ovary were not removed together with the affected horn in order to corroborate by microscopic examination their completely normal gross appearance.

The postoperative diagnosis was that of early rupture of an interstitial tubal pregnancy. Since this type of tubal pregnancy usually ruptures at a much later stage of development, the early catastrophe aroused special interest. After fixation in formalin, section of the tissue removed showed a small cavity filled with blood clot about 7 to 8 mm. in diameter related to the peritoneal surface of the posterior aspect of the left uterine horn rather than to the interstitial portion of the tube. The portion of the horn anterior to the tubal lumen was cut away and the remainder was embedded in paraffin (Fig. 2). Serial sections were cut from the entire involved area, every tenth section being saved and stained. The low power photomicrograph (Fig. 3) showed a section through the central portion of the lesion. The peritoneum on the posterior aspect of

the uterus showed a defect. Beneath this the myometrium contained a rounded cavity filled with blood clot, the peripheral portions of which contain chorionic villi covered with an active well-preserved double layer of epithelium. The central stroma of the villi was made up of edematous embryonal connective tissue. Blood vessels were only occasionally noted. Some of the villi were actively invading the myometrium. No decidual reaction was noted about the implantation site. Only the peripheral villi were present, no evidence being found of a central vesicle. It is believed that this must have been extruded at the time of rupture. In all the sections the mucous membrane of the interstitial tube was intact, as well as the muscularis. At no point did the pregnancy approach the tubal lumen to any closer degree than can

Fig. 3.—Low power photomicrograph showing maternal blood space with rupture through serosa of uterus, and separated from tubal lumen by myometrium, tubal muscle, and mucosa. This space contains blood clot and well-preserved, young chorionic villi, but the central vesicle is absent, apparently having been extruded at the time of rupture.

be seen in the photomicrograph (Fig. 3). From the history, the size of the nidation site, and the appearance of the villi, it is believed that the ovum could not have exceeded four weeks in age. Its early age makes it most improbable that the site of nidation could have been secondary.

COMMENT

These findings give rise to the question as to how this pregnancy occurred in the location described. If it is an interstitial tubal pregnancy the embedding ovum must have traversed the tubal mucosa, the tubal muscle, and a considerable area of myometrium to reach this location. Furthermore it must have accomplished this without leaving a trace of its passage. This is impossible to believe. The only other approach to this location is through primary nidation on the peritoneal surface of the uterus. It is unfortunate that the pregnancy is so closely

adjacent to the interstitial portion of the tube, but this is believed merely to be accidental. This specimen has been presented before the Society of Gynecological Pathologists of New York. It was the consensus of opinion of the members present that it represented a primary peritoneal pregnancy. In closing, it might be pointed out that Ray[18] in 1921 reported from the Bellevue Gynecological Service an identical lesion on the anterior aspect of the uterus just above the bladder fold. This he believed to be an early primary abdominal pregnancy. Unfortunately this pathologic material was scanty and incomplete, in no way as conclusive as in the present specimen.

SUMMARY AND CONCLUSION

An early ruptured pregnancy on the posterior aspect of the uterine horn has been described, which, from its relationship to the peritoneum and to the interstitial portion of the tube, is believed to have reached this location by primary peritoneal nidation.

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Goldzieher and Adler: Estrogen Treatment in a Female Eunuchoid, J. Clin. Endocrinology **1**: 349, 1941.

A case of eunuchoidism and the results of treatment with estrogen are presented. These results are: adequate development of uterus and external genitalia; manifestation of secondary sexual characteristics and establishment of a menstrual cycle; marked development of breasts, attributed mainly to topical administration of estrogen; and striking changes in the general appearance and personality of the patient.

The relationship of infantilism to eunuchoidism is discussed; the latter is defined as a syndrome due to a primary hypogonad state accompanied by secondary hyperpituitarism.

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PSEUDOMYXOMA PERITONEI*

With a Report of Three Cases

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PSEUDOMYXOMA peritonei is an interesting pathologic entity. This condition is characterized by the accumulation of masses of gelatinous pseudomucinous or mucinous material free in the abdominal cavity, and distributed over the peritoneum either as a homogenous layer or in the form of multiple cystic masses. Despite removal of the source and the gelatinous material, repeated reaccumulations may occur, necessitating secondary operations. Ries states, and quotes Werth as stating, that the material must have become part of some organ in the abdomen to be called pseudomyxoma peritonei. It is a relatively rare condition (30 cases in 18 years at the Mayo Clinic, 3 cases in 20 years at the Elizabeth Steele Magee Hospital), seldom seen in patients before the age of 40, and occurring in both males and females, although more commonly in the latter sex.

Peán in 1871 referred to a case of "myxomatous degeneration of the peritoneum" but Werth in 1884 is credited with giving the first description of pseudomyxoma peritonei. Until 1901 it was considered a disease of the female alone, being attributed to rupture of a pseudomucinous ovarian cyst. Then Fraenkel reported a case in a male with the appendix serving as the original focus. Other sources have been claimed; namely, gall bladder, diverticulum of the cecum, umbilical tumor developing from a persistent portion of the omphalomesenteric duct, and dermoid cysts; but in general, the two chief origins are considered to be the ovaries and the appendix. A few cases have been reported in which both a ruptured ovarian cyst and a perforated colloid cyst of the appendix were found. Krivsky is convinced that if both organs are involved, the disease has two distinct and simultaneous places of origin; the one is not a result of the other. Experimentally, pseudomyxoma peritonei has been produced in rabbits both by ligation of the appendix, exclusive of the blood supply, and after irrigation of the lumen, and by the injection of unfiltered pseudomucinous material from a typical case.

This paper deals only with pseudomyxoma peritonei in which the ovaries are the point of origin. Krivsky thinks the prognosis is worse in this form. When a pseudomucinous cyst of the ovary ruptures, the reception of the contents by the peritoneum may be passive with absorption of the contents, or there may occur generalized peritoneal thickening, cellular infiltration, formation of adhesions, proliferation of secondary tumors and formation of multiple cysts; or a combination of

*Presented at a meeting of the Pittsburgh Obstetrical and Gynecological Society, 1942.

all these. There may be a different reaction in different parts of the peritoneum. Large amounts of gelatinous material may form, colored in various shades of red, yellow, brown, or grayish white, depending on the amount of hemorrhage, fatty material, cholesterol, and cellular debris.

The mechanism of the continued formation of pseudomucinous material before or after the removal of the primary source is still a moot question. Possibly there has been alternate rupture and closure of the ovarian tumor. Or does direct implantation of epithelial cells from the lining of the original cyst occur? Only occasionally can epithelial elements be found in the colloid masses, but perhaps the epithelial cells originally implanted are crowded out and disappear after having given rise to mucinous material. Can the peritoneal epithelium assume the function of producing mucus? Or is it a metastasis via the peritoneal lymph or blood stream as is undoubtedly the case in secondary cysts found in the liver and portal vein?

Undoubtedly the character of the myxomatous change in the peritoneal walls will vary with that of the primary new growth. For practical purposes, therefore, there may be considered to be two types of secondary pseudomucinous growth: (1) pseudomyxoma peritonei simplex, a benign passive deposit of the pseudomucinous material in the abdominal cavity; (2) pseudomyxoma peritonei malignum, a transplantation of epithelial cells to the peritoneal surfaces, cells which originally may be malignant or take on malignant characteristics. The distinction between malignancy and nonmalignancy depends upon the degree of recurrence. Thus, some cases can be considered definitely malignant with recurrences in as short a period as a few months, others relatively benign, with no recurrence for years; and still other cases benign when there is no recurrence.

Chemically the gelatinous material is alkaline in reaction. Whether the material is acid when the appendix is the focus and alkaline when an ovarian cyst is the focus as Trotter states, is open to question. Also whether the material is pseudomucin or true mucin as based on its staining reaction with mucicarmine or reduction tests is a valueless distinction; all gradations of staining reactions occur, and reduction tests may be obtained with true mucin.

Clinically pseudomyxoma peritonei presents no inconvenience to the patient until enlargement of the abdomen occurs, as simple rupture of the ovarian tumor does not usually produce any noticeable symptoms. Most patients have symptoms for many months before consulting a physician. The chief complaints are fullness of the abdomen, weakness, dyspnea, frequency of urination, loss of weight, anorexia and often abdominal pain. There may be a history of a previous operation for removal of the appendix or an ovarian cyst. An interval of twenty-two years after the primary operation before the appearance of pseudo-

myxoma peritonei has been noted. The menstrual history may have been regular or irregular. Marital status and parity have no bearing, for whereas all three of our patients were single women, 28 of the 30 patients cited by Masson and Hamrick were married and 21 had had children. Physically the patients usually have a mild secondary anemia, abdominal distention, sallow complexion, and occasionally a cystic mass may be felt on abdominal or pelvic examination.

Treatment consists of two parts: (1) Removal of the source and (2) removal of the pseudomucinous material. Ovarian tumors, whether ruptured or not, should be extirpated, and also the appendix should be removed even if it is so imbedded in gelatinous material that the cecum must be resected. If the uterus is invaded, a hysterectomy is indicated. If there is a nodule in the umbilicus, remove the umbilicus; and if the omentum is involved, it should also be excised. The treatment of the gelatinous material loose in the abdomen and the masses on the parietal and visceral peritoneum is difficult. Washing out is insufficient and complete removal leaves great raw areas. Gentle wiping out is usually resorted to and greater or smaller quantities of material are necessarily left behind. Isolated pseudomyxomatous tumors should be removed as completely as possible. Previous experience dictates that no drains should be left in the abdomen. Finally, x-ray therapy should be given, especially if the pathologist reports malignancy. Hertzler mentions a case in which temporary improvement was coincident with the use of x-ray. Unfortunately, the value of x-ray is neither proved nor easy to evaluate, as the secondary lesions may disappear spontaneously after removal of the source.

It is difficult to be dogmatic about the prognosis of patients with pseudomyxoma peritonei. Ries states that the results of operation may be good at times even though entire masses of gelatinous material could not be removed. He cites a seventeen-year cure. Several cases have been reported of extensive pseudomyxoma peritonei becoming arrested spontaneously and even completely absorbed. There is no explanation for this. Masson and Hamrick believe that if there is no evidence of cancer the outlook is good for permanent cure. Two or threee operations may be necessary. However, with the peritoneum diffusely involved, it is impossible to eradicate the growth, and many patients go downhill so that the condition becomes clinically malignant. To quote Ewing, "the evacuation of this material is sometimes followed by remission, rarely by cure, but usually the condition recurs and persists even when very few tumor cells can be found. Interference with intestinal function by adhesions and strictures terminates the prolonged course of many cases." Novak, Douglass and Faulkner, and Karsner agree on this. It is to be noted that all the latter are pathologists.

CASE REPORTS

CASE 1.—Miss N. S., aged 42 years, small, frail, emaciated white woman, was admitted Jan. 19, 1928, to the hospital with a complaint of

pain in left groin, epigastric fullness, loss of weight and strength. There was a history of feeling weak and tired, having trouble with hemorrhoids, and loss of 18 pounds during past year. There was a sense of fluid splashing about in abdomen. Menopause occurred 2 years previously. For several months epigastric fullness and anorexia were more pronounced. She had to stop work four weeks prior to admission due to weakness. Physical examination showed the abdomen to be rounded and tense with superficial veins prominent. Fluid wave was present. Red blood count was 3,900,000; Hg, 76 per cent; and white blood cells, 7,400. Urine, blood chemistry and serology were negative.

Operation performed on Feb. 1, 1928, revealed a right ovarian multilocular cyst extending 4 cm. above the umbilicus. Several loops of bowel were adherent. The cyst contained a large amount of amber-colored gelatinous material, and this material was also free in the abdominal cavity, even extending up under the diaphragm. The left ovary was small and atrophic. Gall bladder and appendix were not examined. Cyst and gelatinous material were removed. The incision was closed without drainage.

Pathologic Diagnosis: Pseudomucinous papillary cystadenoma of ovary, chronic inflammation of cyst wall.

Postoperative course was uneventful and when seen six weeks following operation, she was feeling well. There was no further follow-up.

CASE 2.—Miss N. H., aged 62 years, thin, frail, white woman, was admitted Sept. 30, 1941, to the hospital with complaint of increasing fullness of abdomen, loss of 15 pounds in past year, and weakness. There was a history of two previous hospital admissions elsewhere: First in 1931 when she had an appendectomy and a right oophorectomy. Pathologic diagnosis: Dermoid cyst of right ovary, multilocular pseudomucinous cyst of right ovary, and chronic appendicitis. Second in 1936 when there was an operation for evacuation of abdominal contents and removal of part of growth. Pathologic diagnosis: Papillary pseudomucinous cystadenocarcinoma of right ovary. Physical examination revealed a tense abdomen with evidence of fluid, and on vaginal examination there was a soft mass in the cul-de-sac and pelvis, or rather multiple small masses.

Red blood count was 4,300,000; hemoglobin, 76 per cent; and white blood count, 4,450. Urinalysis, serology, and blood chemistry were negative.

Operation performed Jan. 2, 1941, revealed two previous laparotomy scars which were excised. Peritoneum was markedly thickened and on the right side of the abdomen there appeared to be a secondary abdominal cavity well walled-off and filled with a yellowish gelatinous material. Seven quarts of this material were removed, and a biopsy was taken of the peritoneum. Abdomen was closed without drainage. Pathologic diagnosis: Peritoneum and skeletal muscle without evidence of tumor, pseudomyxoma peritonei.

Postoperative course uneventful. Patient appears well four months later. X-ray treatments have been given.

CASE 3.—Miss B. S., aged 55 years, a well-developed, well-nourished, pale Jewish female, was admitted to the hospital on Sept. 25, 1928, with chief complaint of mass in abdomen of one years' duration, and progressive weakness. She had been operated upon in another hospital five years previously for "flooding spells." She had a dilatation and

curettage, bilateral salpingo-oophorectomy, and appendectomy. Pathologic diagnosis: Pseudomucinous ovarian cyst, chronic peri-oophoritis.

Physical examination revealed a distended abdomen with a cystic mass on the left side. Red blood count was 3,840,000; hemoglobin, 78 per cent; and white blood count, 10,800. Urinalysis, serology, and blood chemistry were negative.

She was given a transfusion, and operation was performed on Oct. 1, 1928. "Half a pus basin" of pseudomucinous material was removed, also a left cystic structure considered to be part of left ovary and cystic mass of omentum was removed. Pathologic diagnosis: Pseudomucinous multilocular cystadenocarcinoma of ovary and omentum. Postoperative course was uneventful. She remained in hospital twenty-eight days.

Second Admission, April, 1931.—She felt well until previous summer. Since then there had been a gradual reaccumulation of fluid in the abdomen, increasing weakness, fatigue, and pressure symptoms.

At operation on May 1, 1931, 4,800 Gm. of orange-colored pseudomucinous material and a piece of peritoneum were removed.

Pathologic diagnosis: Peritoneum with chronic inflammatory reaction.

Postoperative course was uneventful. She was in the hospital fourteen days.

Third Admission, September, 1931.—The abdomen had begun to swell shortly after leaving the hospital in May. She was readmitted to drain abdomen. At operation on Sept. 10, 1931, four gallons of gelatinous material were removed. Biopsy of peritoneum was made. Pathologic diagnosis: Papillary cystadenoma malignum of ovary.

Postoperative course was uneventful. She was in the hospital twenty-nine days.

Fourth Admission, January, 1933.—There was marked improvement following the last operation, and her state of health has been better than at any time in years. A cyst is still present in the left lower quadrant, the size of a grapefruit. She is so much improved following last operation that she was admitted to attempt a removal of what was probably the primary growth. At operation on Jan. 30, 1933, intestines were matted together and involved in a recurrence of the papillary cystadenocarcinoma. Large quantity of thick jelly-like, yellowish material was removed. Supravaginal hysterectomy was done. The tumor growth was removed from remnants of omentum, peritoneum, colon, liver, and mesentery of small intestine. Colon was perforated.

Pathologic diagnosis: Atrophic endometrium, chronic metritis with arteriosclerosis, adenomyoma of uterus, and papillary cystadenoma, secondary. Complication: fecal fistula. Remained in hospital twenty-eight days.

Fifth Admission, December, 1935.—Patient felt well up until a few months ago. Since then there had been fullness and discomfort in the abdomen, anorexia, weakness, and diarrhea. Physical examination showed a very pale, well-developed, well-nourished, white female of 64 years. Abdomen was dome shaped. Irregular mass was palpable in the upper abdomen.

Red blood count was 3,300,000; hemoglobin 67 per cent; and white blood count, 9,400. Blood chemistry was negative. Urinalysis showed 1+ albumin.

At operation on Dec. 10, 1935, the intestines were found to be studded with small tumorous nodules; spleen was enlarged and covered with

tumorous growth; and 4½ pounds of gelatinous material were removed. Pathologic diagnosis: Pseudomyxoma peritonei.

Postoperative course was uneventful. She was in the hospital twenty-one days.

This patient was admitted to another hospital about six months later and died in October, 1936, of intestinal complications resulting from the abdominal tumor.

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CHORIONEPITHELIOMA*

An Unusual Case in Which Cerebral Metastasis Occurred Four Years After Hysterectomy

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WITH considerably more than 2,000 records of chorionepithelioma in the medical literature, an introductory apology is perhaps necessary before we add another. The following unique features in our case would appear to justify inclusion of it among the more unusual and interesting examples of this rare form of malignant process: (1) a four-year period of latency between removal of the primary neoplasm and the appearance of secondary lesions, (2) cerebral symptoms as the first indication of metastasis, and (3) a negative reaction to the Friedman test.

REPORT OF A CASE

A woman, 29 years old, came to the clinic in July, 1941, complaining of headache, weakness, and double and blurred vision. Two and one-half weeks previous to her examination, she had noticed rather rapid loss of vision, until only the gross form of objects could be seen. There was marked loss of balance with staggering, but the patient did not fall. Thereafter, blurring of vision recurred frequently. Two weeks prior

*Submitted for publication, March 30, 1942.

to registration at the clinic, she had begun to experience severe headache at the occiput and vertex, as well as pain in both eyeballs. This pain was associated with stiff neck and ringing, pounding tinnitus in both ears. A week prior to her entering the clinic, nausea and vomiting had begun but were not definitely associated with the headache. Her symptoms had progressed to such an extent, she remarked, that three days before her examination at the clinic she thought she was "going to die," because she had experienced numbness of both hands and arms, and then a wave of numbness, so to speak, over the whole body.

In giving her history the patient stated that in August, 1937, the uterus had been removed after a diagnosis of "hydatid mole" complicating pregnancy. There had been, she was assured, no penetration of the uterine wall. No symptoms had arisen to indicate recurrence of the process locally in the pelvis.

The sudden onset of severe and evident intracranial pressure was very suggestive of tumor of the brain and because of the previous lesion in the uterus, a metastatic malignant process was considered in the preliminary diagnosis. The interval of four years between hysterectomy and the current symptoms, however, seemed to point against recurrence of this type of neoplasm.

Upon examination, the patient was found to have complete left homonymous hemianopia with enlarged blind spots and bilaterally choked disks (elevation of 2 diopters), with hemorrhage of some extent. Neurologic examination revealed some degree of weakness of the left side of the face and of the left extremities, and there was a slight increase in reflexes on the left side. Roentgenologic examination of the head disclosed questionable shifting of the pineal gland toward the left. The electroencephalogram demonstrated a delta localization in the right posterior temporooccipital region. The results of other examinations, including pelvic examination, were negative. A diagnosis of primary tumor of the brain was made and operation was advised for removal of a tumor of the right temporal lobe.

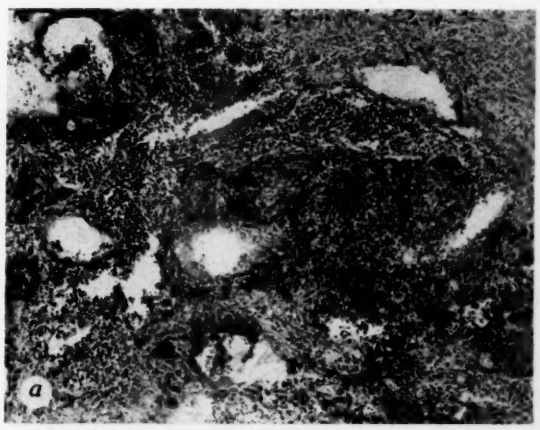
Operation was carried out on Aug. 5, 1941. With the patient under the influence of intratracheal anesthesia, right craniotomy was performed. The convolutions of the temporal lobe were flattened and broadened in the posterior aspect. A mass was found subcortically, and when the cortex was incised, a dark, vascular nodule about the size of a large plum (Fig. 1) was found, at a depth of about 3 cm., extending posteriorly into the occipital lobe. The tumor "shelled out" after the manner of a metastatic lesion, and grossly suggested chorionepithelioma.

After an uneventful convalescence, the patient was allowed to return to her home on the tenth postoperative day. The wound had healed well and the patient was completely relieved of her headache. She still had homonymous hemianopia, however. In a recent communication from the physician in attendance we learned that the patient died on Sept. 19, 1941. There was no necropsy.

Histopathologic Observations.—Grossly, the tumor was 6 by 4 by 3 cm., was brownish red, and seemed to have separated cleanly from the surrounding brain tissue. The cut surface demonstrated the nodule to be hemorrhagic, a feature somewhat unusual for cerebral metastasis of chorionepithelioma.

In microscopic sections made by the rapid freezing technique and stained with polychrome methylene-blue, large masses of pale-staining cells were seen. These were manifestly malignant. Intermingled with

Fig. 1.—Metastatic chorionepithelioma. The dark color and apparent encapsulation are evident.



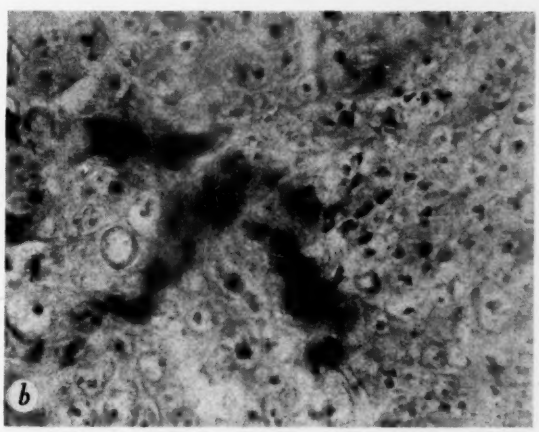


Fig. 2.—*a*, Chorionepithelioma of the brain. The dark staining masses of syncytial cells stand out in contrast to the pale-staining Langhans cells; tumorous tissue is demarcated from the normal brain by a zone of inflammatory cells (hematoxylin and eosin ×70). *b*, Chorionepithelioma of the brain, showing the malignant syncytial (dark) and Langhans (pale) cells in the absence of villous structures (hematoxylin and eosin ×415).

these cells were observed irregular sheets of malignant syncytial cells with abundant cytoplasm and large hyperchromatic nuclei. Glial fibers, always identifiable by the aforementioned method of examination, were not observed. The picture, briefly, was that of a metastatic Grade 4 neoplasm, and was entirely compatible with a diagnosis of chorion-epithelioma. Immediately after operation urine was collected on a quantitative basis, for determination of prolan according to the Friedman technique. Results of this test later were reported as negative for excess amounts of the hormone.

Fixed frozen sections made the day after operation on formalinized blocks of tumor tissue confirmed our earlier diagnosis of metastatic chorionepithelioma. The photomicrographs (Fig. 2, *a* and *b*) depict the characteristic features.

COMMENT

Chorionepithelioma is a rapidly fatal form of cancer. According to Ewing, the disease usually lasts for from six to eighteen months (with or without hysterectomy). In at least one case it has progressed to fatal termination within thirty-four days of the inception (so far as could be determined) of the lesion. It is most surprising, therefore, to encounter a case like ours, in which there was such a prolonged "latent period." Outerbridge, in an excellent review of this phase of the subject, mentioned some 25 reports of cases in which there was a latent period of more than two years, and 9 cases in which a period of five years or more had elapsed before "recurrence" became manifest clinically. This author admitted, however, the difficulty of establishing with certainty the exact date at which the primary tumor originates. Chorionepithelioma is a complication of pregnancy, but the actual pregnancy which is concerned with the development of the neoplasm may be "concealed" and occur during the supposed latent period. According to Brown, Snodgrass and Pratt, the duration of this latent period can be established accurately only when it follows hysterectomy for the primary neoplasm. These authors presented such a case. Their patient died as a result of metastatic chorionepithelioma nine years after removal of a hydatid mole and seven years after performance of hysterectomy in which a residual primary tumor had not been disclosed. The case recorded by Cary would have a similar category. Spinal metastasis developed three and one-half years after hysterectomy for chorion-epithelioma. Dunger's patient died of cerebral metastasis three years after expulsion of a "mole." To this small group belongs our example, in which the so-called latent period of four years is established on a basis of certainty. The explanation for these delayed recurrences in a tumor so manifestly malignant is beyond the present scope of our knowledge. It is paralleled by the still stranger observations of regression of metastasis as occasionally noted in this strange disease.[7]

The incidence of cerebral involvement in chorionepithelioma is difficult of establishment. Clinical symptoms are at times misleading and permission for examination of the brain often is withheld when the patient comes to necropsy. Polasson and Violet listed the incidence of cerebral metastasis as being 9 per cent in a series of 455 cases which included all types of chorioma. Brews reported a series of 14 cases in which the disease was fatal; evidence of cerebral involvement was present in 5 and such involvement was proved by complete necropsy in 4. These figures,

although they are higher than the 5 per cent incidence quoted by Green, will still be low when data from complete necropsy become available in large series of cases. Lynch and Maxwell noted a characteristic tendency for localization of metastatic deposits in the occipital lobes. In our case the right occipital lobe was involved, but apparently by a process of extension from a deposit in the temporal convolutions.

Pulmonary involvement, probably always a prerequisite to cerebral metastasis in chorionepithelioma, was not demonstrated by roentgenograms in our case. Peightal, however, recorded an instance in which, with the lungs described as being roentgenographically negative, metastatic deposits were demonstrated therein at post-mortem examination. We hesitate, therefore, in our case, to inject the interesting possibility that the pulmonary focus had disappeared. The inescapable fact of a four-year dormancy in this highly malignant neoplasm carries with it sufficient of the unusual.

The negative reaction to the Friedman test, interesting as it is remarkable, in no wise nullifies our diagnosis in this case. All authorities agree that a *positive* reaction in cases of chorionepithelioma is of prime importance diagnostically as well as prognostically. The reverse, however, is not the case, and many investigators have recorded instances of proved chorionepithelioma in which a single reaction to the Friedman test was negative, or in which a series of positive reactions was interrupted by an occasional negative reaction. Most gynecologists and probably all pathologists will agree with Novak, who asserted that the final diagnosis of chorionepithelioma rests with the microscopist. Admitting that such a diagnosis may be difficult in the case in which only small fragments of tissue or curettings from the uterus are available, histologic evidence of distant metastasis certainly settles the question for all concerned.

SUMMARY

A case of chorionepithelioma is presented in which a latent period of four years had elapsed between the removal of the primary tumor and the development of clinical metastasis. The date of inception of the disease was established by the time of a previous hysterectomy. Pathologic proof of cerebral metastasis was furnished by examination of the lesion at biopsy. Urine collected shortly after craniotomy gave a negative reaction to the Friedman test.

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HYDATID MOLE WITH A HIGH PERSISTENT TITER OF GONADOTROPIC HORMONE*

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R. M. D., a white married woman 27 years of age, was admitted to the surgical ward of the Episcopal Hospital on Dec. 10, 1940. Her chief complaints were vaginal bleeding and pain in the lower abdomen. Her last normal menstrual period had begun on Sept. 1, 1940, and lasted five days. She had missed her October period. Shortly thereafter she began to experience nausea combined with some sensations of pregnancy. She said that on Nov. 15, 1940, she had lost about a cupful of blood from the vagina within a half hour, but that no further bleeding occurred until December 2, when a little spotting was noted. She again began to bleed on December 5. She is the mother of one child three years of age. There was no other significant medical history.

Inspection on admission revealed a mass which extended above the umbilicus. The mass was movable and not tender, and was believed to be a pregnant uterus. A vaginal examination was not made, since the tentative diagnosis was threatened abortion. Her blood on admission showed 64 per cent hemoglobin and a leucocyte count of 11,000.

I was asked to see the patient in consultation on Dec. 12, 1940. At that time a bimanual examination was performed, and it was noted that the uterus was enlarged to the size of a four and one-half months' pregnancy and that there was no discharge of any nature coming through the closed cervix. At the time of the examination she complained of considerable abdominal pain and looked far whiter than her relatively normal blood count, made on admission, would seem to warrant. I suggested her transfer to the maternity department and made a tentative diagnosis of hydatid mole. Studies of the blood and urine were ordered, and these subsequently confirmed the diagnosis. The patient, however, impressed me as being so anemic that I thought it unwise to wait for the results of these studies to be reported, and immediately began to prepare her for evacuation of the suspected mole. During the next two days she was given transfusions totaling 1,000 c.c. of blood. At this time she was exceedingly distressed with abdominal pain and appeared critically ill.

Evacuation of the mole was performed manually on Dec. 15, 1940, under light ether anesthesia. The entire mole, which amounted to several quarts of grapelike clusters, was removed. There was present in the growth, in addition to the hydatid material, a large number of old and new blood clots.

On the following day the interior of the patient's uterus was gone over lightly with a blunt curette to make sure that complete evacuation had been accomplished. No additional material was obtained.

Convalescence, which was aided by another blood transfusion, was uneventful. The patient was discharged from the hospital on December 29, her blood picture having responded very satisfactorily to the usual treatment.

*Presented at a meeting of the Obstetrical Society of Philadelphia, December 4, 1942.

She was referred to the Curtis Clinic of the Jefferson Medical College on February 10, 1941, for quantitative hormonal studies of the blood and urine. Specifically, 330 mouse units of quantitative serum gonadotropin per 100 c.c. of blood were found, and the Friedman test was positive in a dilution of 1 to 10. A re-check two weeks later gave precisely the same high values.

In view of these laboratory findings and the possibility of persistence of the mole or the development of a chorionepithelioma, the patient was re-admitted to the Episcopal Hospital on Feb. 27, 1941. On February 28, under general anesthesia, a diagnostic dilatation and curettage was performed, the latter with a sharp curette. No material of any kind was obtained and there was no bleeding. A check made upon her blood showed 4,300,000 erythrocytes per c.mm., with a hemoglobin value of 80 per cent. She was afebrile throughout, and an x-ray of her chest gave no evidence of pathologic change.

Another study of the patient's blood and urinary hormones in March revealed, to our surprise, the same high titer as in previous tests. A still later study on May 16, however, disclosed that the gonadotropic hormones were then entirely normal in amount.

The patient's menstrual periods returned and, to date (Nov. 21, 1941), have continued normal. The results of a Friedman test made in October have been reported as negative and she is in excellent health.

DISCUSSION

DR. A. E. RAKOFF.—I had the opportunity of making the usual hormone assays on this patient during the interval stated. I think the elementary assays which are shown here bring up several points of interest. As Dr. Toland stated, shortly before the uterus was emptied, because of the clinical diagnosis of hydatidiform mole, the serum gonadotropins were very high. That, of course, raises the question as to the value of gonadotropic assays for the diagnosis of hydatidiform mole. Many of these tests were done which at least encouraged us to make an absolute diagnosis of mole on this basis. When we first began making the assays in patients of all kinds, in the first 50 in normal pregnancies, I came to the conclusion that the high value about the third month of pregnancy is usually about 2,000 M.U. per c.c. When the series reached 100, I thought 10,000 occasionally is encountered, and recently we have found in normal pregnancies values as high as 20,000, and that was in a case of suspected hydatid mole. The patient was not operated upon because the attending physicians felt it was not a mole, and their opinion was confirmed. The moral is that this is a laboratory test, is only one piece of evidence, and we do not know how high the serum gonadotropin may go in normal pregnancy. During the first half, they may reach quite high levels, although this value seems to be high enough to be safe. The next factor of interest was after the uterus was emptied, the Friedman test remained positive. This must be viewed with caution because we have found not infrequently that the test may remain positive after a normal delivery in normal patients. Why, I cannot say except pregnancy gonadotropin gradually falls off, and there may be some retained placental tissue viable. The next interesting factor was that the gonadotropin tended to rise somewhat. It would seem here that in time the gonadotropin were at least slightly on the increase and not on the decrease, and the usual assumption is that we are dealing possibly with a chorionepithelioma. In this case this persisted three months, despite the fact that no material was obtained on curettage. The following month the patient menstruated and the gonadotropin returned to normal. What the interpretation is, I cannot say. It does not seem due to the fact that the body is unable to excrete this high amount of gonadotropin. The one assumption is that there was active chorionic tissue present.

DR. WALT P. CONAWAY.—In June of this year a young girl, aged 19 years, single, was admitted to the gynecologic ward of the Atlantic City Hospital on another service with a diagnosis of hydatid mole. The diagnosis was confirmed and the uterus was emptied with a curette. She made a good recovery and was discharged in about a week.

In July she felt well and the latter part of that month she menstruated five days, apparently normal. At this time the Friedman test was negative. In August and September there was complete amenorrhea but about the middle of October she began to have a bloody discharge with some pieces of tissue. The pain increased for the next few days and she was re-admitted on November 1, this time on our service. Although the uterus was about the size of a ten to twelve weeks' pregnancy, a diagnosis of hydatid mole was made and emptying of the uterus was advised. On account of the severity of the pain and the bloody discharge, a diagnosis of chorionepithelioma was considered. The uterus was again emptied with a curette and the contents proved to be another mole with no evidence of epithelioma. A Friedman test was positive at the time of operation. She bled very freely and a blood transfusion was necessary. After this she made a prompt recovery and was discharged from the hospital in about ten days.

DR. ALBERT P. DAVIS.—I saw two cases of mole this summer, one malignant and one not. The patient with the malignant lesion completed an abortion of the mole on May 26, and kept bleeding off and on, and irregularly, until August 4 when a Friedman test was done which was strongly positive. She re-entered the Hospital, and an hysterectomy was done on August 28. The uterus was about normal in size but in the wall were buried cystic tumors which proved to be a malignant mole on laboratory examination. This patient had another Friedman test on October 27, which was negative. A test before she left the Hospital on September 10 was negative, and another on October 27 was negative, and she now seems to be well.

The other was a case along about the same time. When I first saw the patient she was about three and one-half or four months pregnant. She had had normal children. I suspected a mole because of the condition of the uterus. She was sent into the Hospital. There was no discharge of any great quantity. A Friedman test was negative, and a curettage was done on August 14. An hysterectomy was performed. The test was negative on October 4, and she has remained well. As far as the gross specimen was concerned it was much more positive than the other specimen.

DR. TOLAND (closing).—This case history is presented in order to act as a deterrent to the surgical enthusiasm of those who might desire to remove a uterus shortly after the evacuation of a hydatid mole, merely because a high urinary prolan exists. This report is entirely corroborative of the observations of Payne in his published report of 54 cases of hydatid mole in which urinary prolan was determined after the evacuation or expulsion of the mole, and the patient completely recovered. In his series, which consisted of 8 of his own and 46 collected from the literature, he showed that in all but 5 of the cases, the urine was test negative within eight weeks but that 4 per cent showed positive reactions longer than twelve weeks.

My own case is corroborative of his conclusions that the urinary hormone level will usually return to normal within three months following the termination of a mole pregnancy, "but an abnormal level that persists for a longer time does not necessarily indicate the presence of a chorionepithelioma, provided the level does not rise during this time."

THE ELDERLY PRIMIGRAVIDA*

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THE obstetrician is called upon from time to time to assume responsibility of a case of pregnancy when the woman is having her first baby late in her reproductive life. Both common teaching and experience have led to the belief that the elderly primigravida will have a difficult labor. It has been our experience, however, that because the bony pelvis, from an obstetric point of view, is fixed by the time the young woman enters the childbearing period and the soft parts likewise retain their texture during the entire reproductive period, mere age has a trivial influence on the type of labor.

This study was made in a voluntary hospital with a closed staff (where the majority of cases are handled by general practitioners), in an effort to determine whether there is an increased risk in the labor of the "elderly primigravida." In this group is included the woman thirty-five years of age or over who is pregnant for the first time.

INCIDENCE

There were 111 such cases among 10,233 deliveries in four and one-half years. The age distribution is given in Table I; the majority were in the 35- and 36-year age group. The pelvis was normal in 103 cases and contracted in 8. It is significant to note the high incidence of normal pelves in this group of elderly patients.

DURATION OF LABOR

It has repeatedly been stated and indeed it is the common belief that the duration of labor among old primigravidas is usually longer than in the young patient. This is not borne out in this series of cases. The average labor was 18.9 hours (Table I), and is in accord with previous reports of Quigley.[1]

TERMINATION OF LABOR

Labor terminated spontaneously in 49 per cent of the cases in this series (Table II), while the low forceps operation was employed in 28 per cent. It must be remembered that low forceps is a very common elective procedure in many primigravidas and is practiced frequently. Hence, the number of cases terminated by low forceps should not be overemphasized in the final conclusions. When one investigates the incidence of major obstetric procedures, the following data are evident. Mid-

*Read at a meeting of the Bronx Gynecological and Obstetrical Society, April 27, 1942.

TABLE I. SUMMARY OF THE CASES

AGE IN YEARS	NO. OF CASES	TYPE OF PELVIS		AVERAGE HOURS IN LABOR	TERMINATION OF LABOR						OBSTETRIC MORTALITY		
		NORMAL	CONTRACTED		SPONT.	LOW FORCEPS	MID-FORCEPS	CESAREAN	BREECH EXTR.	VERSION	MATERNAL	STILLBIRTHS	NEONATAL
35	35	31	4	19.6	17	10	5	3			1	2	
36	25	25		24.9	11	8	1	4	1			3	1
37	19	19		18.9	13	3	1	2				1	1
38	13	10	3	28.3	4	2	3	3		1	1	1	
39	5	5		10.7	4	1					1		
40	8	8		22.5	4	4						1	
41	4	3	1	14.3	1	3							
42	2	2		12.3	1			1					
Totals	111	103	8	18.9	55	31	10	13	1	1	3	8	2
%					48%	28%	9%	11.7%			2.7%	9%	

forceps operations were employed in only 9 per cent of the cases, all in the second stage; 3 cases for persistent occiput posterior; 3 cases for sudden fetal distress; and 4 cases for lack of progress due to maternal inertia (Table II).

Breech presentation occurred four times: 3 were delivered spontaneously and in one case extraction with Piper forceps to the aftercoming head was done.

Cesarean section was performed in 13 cases, or 11.7 per cent. This is in accord with the results of Nathanson[2] and Daichman.[3]

The indications for the operation are shown in Table II. In 5 cases the operation was performed because of contracted pelvis; in 3 because of a pregnancy complicating a fibroid uterus; and in 2 cases because of cephalopelvic disproportion. All of these patients had a definite test of labor and the indication for the operation was not the advanced age of the patient. The 3 other cases were elective operations; 2 cases for uncontrollable toxemia, one case for a known cervical stenosis due to a previous cervical amputation.

TABLE II. OPERATIVE CASES

OPERATIVE INDICATIONS	OPERATIVE PROCEDURES					OBSTETRIC MORTALITY	
	LOW FORCEPS	MID-FORCEPS	CESAREAN	BREECH EXTR.	VERSION	MATERNAL	FETAL
Head on perineum one hour or more	17						1
Persistent O. P. or O. T.		3					
Full dilatation for two hours without progress	3	4					3
Sudden fetal distress	11	3			1		
Frank breech				2			
Contracted pelvis			5	1		1	1
Fibroid uterus			3				
Toxemia			2			1	
Cervical stenosis			1			1	
Cephalopelvic disproportion			2				

While an incidence of 11.7 per cent for cesarean section may at first appear to be high and almost suggestive of radical obstetrics, nevertheless, it is of utmost importance not to lose sight of the fact that in the case of the elderly primigravida so much is at stake that everything ought to be done to obtain a living child. It is interesting to compare the results obtained by the so-called conservative clinics. Nixon,[4] of London, reported a series of elderly primigravidas in whom no cesarean sections were performed. Here there was a maternal mortality of 4 per cent and a fetal mortality of 17 per cent; this is a maternal and fetal mortality one and one-half and two times as high, respectively, as that to be reported in this study, notwithstanding our cesarean incidence of 11.7 per cent. Nixon is frank to admit that the operation should have been resorted to oftener in his series of cases. Linden,[5] of Stockholm, who also follows ultraconservative procedures, reports a series of cases in elderly primigravidas in whom craniotomy was performed in 4 per cent of the cases but with no maternal deaths. In our cases the high incidence of cesarean section seems justified. It is evident from the tables that 88.3 per cent were delivered per vaginam.

Post-partum hemorrhage occurred only once. The patient was treated by uterine packing and transfusion and had an uneventful puerperium.

MATERNAL MORTALITY

Three deaths occurred in this series of cases, a mortality of 2.7 per cent. Strikingly enough, they all occurred in patients who were delivered by cesarean section. An analysis of these cases, in all of whom necropsy was performed, showed the following:

1. Death four hours after an operation undertaken for a severe uncontrollable pre-eclampsia. Necropsy showed evidence of liver and kidney damage.

2. One woman died of a bronchopneumonia following evisceration of the abdominal wound on the seventh day post-partum. Necropsy showed bronchopneumonia.

3. One patient died from paralytic ileus without peritonitis. Paralytic ileus was found at post-mortem examination.

TABLE III. OBSTETRIC MORTALITY

TYPE OF DELIVERY	NECROPSY FINDINGS						
	MATERNAL			FETAL			
	PRE-ECLAMPSIA	PARALYTIC ILEUS	BRONCHOPNEUMONIA	MACERATED	CEREBRAL HEMORRHAGE	PREMATURITY	?
Spontaneous				3	1	1	
Low forceps				1			
Midforceps					1		1
Version					1		
Cesarean section	1	1	1				1

FETAL MORTALITY

There were eight stillborn infants and two neonatal deaths, giving a fetal mortality of 9 per cent. Four of the stillborn infants were macerated. Excluding these cases, the corrected fetal mortality is 5.4 per cent, an incidence that is at least twice as high as previously reported by us[6] in another study of 10,000 cases at the Bronx Hospital. The fact that this incidence is twice as high entitles it to an important place in the conclusions of this study, whatever causes we may assign to it as an explanation.

SUMMARY AND CONCLUSIONS

1. Labor definitely was of no longer duration in the old primigravida.

2. Cesarean section was performed in 11.7 per cent of the cases. It is of utmost importance to note that the age of the patient was not the major indication for the operation, such potent contributing factors as pelvic deformity, progressive toxemia, etc., being present in the cases of the elderly primigravidas in whom cesarean section was performed.

3. The fetal mortality incidence was twice as high among the children born to the older patients as compared with a previous study of 10,000 cases.

4. The maternal mortality was 2.7 per cent.

5. In the last analysis, on the basis of this study, no inflexible rules can be laid down for the routine conduct of labor in elderly primigravidas. Individualization of each case with its concomitant demands would appear to be the only ideal approach to the solution of the problem.

We are indebted to Dr. Meyer Rosensohn for his helpful criticisms in the preparation of this report.

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1229 Clay Avenue
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INCIDENCE OF PLACENTA PREVIA DURING A TEN-YEAR PERIOD AT CLEVELAND MATERNITY HOSPITAL (1931-1940)*

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MEDICAL literature has always been full of references to placenta previa. As early as the seventeenth century writers on obstetric subjects accurately described this complication, and its presence has always demanded the wholesome respect of all obstetricians.

Placenta previa is said by leading authorities to occur in from 1 in 200 cases to 1 in 2,000 cases. In the series which we are presenting, those occurring at the Cleveland Maternity Hospital in a ten-year period from 1931 through 1940, the incidence was 160 in 20,498 cases, or one in 128 cases (0.8 per cent). This high incidence is due to the fact that our cases included most of the patients hospitalized from our out-patient department; if the 19,374 deliveries from this department are included, the actual incidence was far less (1 in 249 cases). Of the cases of placenta previa only 19 patients (12 per cent) were Negroes.

Fifty-nine per cent of the patients had no bleeding previous to that for which they were admitted to the hospital. Sixty-seven patients (42 per cent) had pains with bleeding and 21 (13 per cent) were in profound shock. The blood loss was small in 59 cases (37 per cent), moderate in 80 cases (50 per cent), and large in 21 cases (13 per cent). Forty-four patients (27.5 per cent) required transfusions before, during, or immediately after, delivery.

*Read at a meeting of the Section of Obstetrics and Gynecology of the Academy of Medicine, Cleveland, Ohio, December 17, 1941.

In 43 cases (27 per cent) the type of previa was lateral; in 78 cases (49 per cent), it was marginal, and in 39 cases (24 per cent), it was central. The ages and parity of the 160 patients are shown in Tables I and II.

TABLE I. AGE OF PATIENTS

	NUMBER OF CASES	PERCENTAGE
10 to 19 years	11	7
20 to 29 years	69	43
30 to 39 years	71	44
40 to 49 years	9	6

TABLE II. PARITY

	NUMBER OF CASES	PERCENTAGE
Para i	52	33
Para ii	40	25
Para iii	19	12
Para iv	19	12
Para v	13	8
Para vi to xiii	17	10

Pregnancy was complicated in 20 per cent of the cases. The three complications found most frequently were fibromyomas of the uterus, toxemia of pregnancy, and heart disease. It is of interest that three of the patients with previa had had a previous section, and of these two had had previa with the first section.

There were 143 (87 per cent) vertex presentations, 18 (11 per cent) breech presentations, and 3 (2 per cent) transverse presentations. There were 4 sets of twins.

Table III shows the type of delivery used in these cases. In 121 cases (76 per cent) cesarean sections were done. Since 1935 the trans-

TABLE III. TYPE OF DELIVERY

	NUMBER OF CASES	PERCENTAGE
Cesarean sections:		
1. Transverse laparotrachelotomy	48	30
2. Longitudinal laparotrachelotomy	16	10
3. Low classical section	43	27
4. High classical section	12	8
5. Porro section	2	1
(Total sections 121, 76 per cent)		
Other methods:		
6. Forceps	19	12
7. Internal podalic version	8	5
8. Spontaneous	6	4
9. Breech extraction	4	2
10. Braxton Hicks' version	1	0.5
11. Vaginal hysterotomy	1	0.5

verse laparotrachelotomy has been the most common type of section that we have done in this hospital. In the patients not treated by section manual dilatation was done in 4 (2 per cent), and the Voorhees' bag was used in 3 (1.8 per cent).

The maternal morbidity was 37.5 per cent. The causes of morbidity are listed in Table IV.

TABLE IV. MATERNAL MORBIDITY, 60 CASES (37.5 PER CENT)

CAUSES	NUMBER OF CASES	PERCENTAGE
1. Cause unknown*	24	40
2. Wound infection	13	22
3. Pelvis	12	20
4. Genitourinary	9	15
5. Respiratory	5	8
6. Phlebitis	5	8
7. Peritonitis	2	3
8. Appendicitis	1	2

*The fever in these cases was of short duration and was not severe.

TABLE V. FETAL MORTALITY

WEIGHT AT BIRTH	DEATHS	STILL-BIRTHS	TOTAL	PERCENTAGE
Below 1,500, nonviable	12	5	17	41
1,500-2,500, premature	11	4	15	37
Above 2,500, full term	4	5	9	22
Total	27	14	41	100
Percentage	66	34	100	---

The fetal mortality is shown in Table V. The uncorrected fetal mortality rate was 25 per cent (41 deaths in 160 cases). If from this number the nonviable cases and premature deaths are excluded, the corrected fetal mortality was 8 per cent (14 deaths in 168 cases). There were two maternal deaths (1.25 per cent). The first patient had a Porro section; peritonitis and wound disruption developed and the patient died on the twelfth day. In the second patient a classical section was done. Intestinal obstruction and peritonitis developed and laparotomy was carried out on the tenth day. The patient died on the seventy-ninth day with thrombophlebitis and pneumonia.

SUMMARY

In the ten-year period from 1931 through 1940, there were 160 cases of placenta previa in 20,498 patients admitted to our hospital (0.8 per cent).

The greatest number were between 20 and 29 years of age, and one-third of them were primiparas.

All of these patients showed bleeding upon admission and 67 (42 per cent) had pain. Twenty-one (13 per cent) were admitted in pro-

found shock. Forty-four (27.5 per cent) required transfusions before, during, or immediately following delivery.

Sixty-seven per cent were delivered by cesarean section. In the first few years the classical section was commonly performed, but since 1935 the transverse types of laporatrachelotomy has been utilized more and more.

Braxton Hicks' version was used only in one case in which the child was not viable. The Willetts clamp was never used.

The gross maternal morbidity was 37.5 per cent, and the uncorrected fetal mortality was 25 per cent, and there were two maternal deaths (1.25 per cent).

2105 Adelbert Road

ADENOACANTHOMA WITH OVARIAN METASTASES

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ADENOCARCINOMA of the fundus with squamous cell metaplasia is not uncommon. Miller[1] found it in 15 per cent of his cases, while Novak[2] states that it is occasionally seen. The phenomenon is not clearly understood but Novak accepts the origin as from "indifferent" cells "possessing a differentiating potency which under certain conditions can lead to the formation of a squamous type epithelium."

The occurrence of ovarian metastases with fundal carcinoma is uncommon. However, Barnes[3] found it in 7.4 per cent of his cases, Norris and Vogt[4] in 1.7 per cent, and Novak[2] in 4.8 per cent. More uncommon is the appearance in the ovarian metastases, of metaplastic elements with keratin formation. The only other case we have been able to find is the one reported by Schattenberg and Ziskind,[5] which was a far-advanced growth.

The prognosis in adenoacanthoma is apparently little influenced by its strange pathologic picture, although Meigs[6] does not agree in this. The prognosis with ovarian metastases, if not present elsewhere, should be good.

The general lack of appreciation that early carcinoma of the fundus can and does metastasize to the ovary should be a warning to those who advocate only radiation therapy.

CASE REPORT

H. S., a married, white, multipara, aged 50 years, first came to my (C. T. B.) office on Jan. 16, 1942, with a chief complaint of vaginal discharge. Her family history revealed that a brother and a sister had died of "cancer of the bowel." Her past history was not significant. Onset of catamenia was at 12 years of age, with a twenty-eight-day cycle, lasting five days. She had had two pregnancies (last in 1922), terminated with forceps deliveries at term. Five years ago (1937)

patient began having hot flushes and insomnia, associated with grossly irregular periods. One and one-half years ago she began to spot every day with never anything suggesting a menstrual period. This bleeding stopped in October, 1941, and since then patient had noticed a profuse, serous, malodorous discharge. There was no bleeding of any kind after October, 1941.

Physical examination was essentially negative.

Pelvic examination revealed only a small nodule (3 cm.) at the left cornu of the uterus. This we believed was a myoma.

Jan. 19, 1942: Admitted to Temple University Hospital and a curettage was done. Uterine cavity was found to be three inches deep. Abundant pinkish gray tissue was obtained.

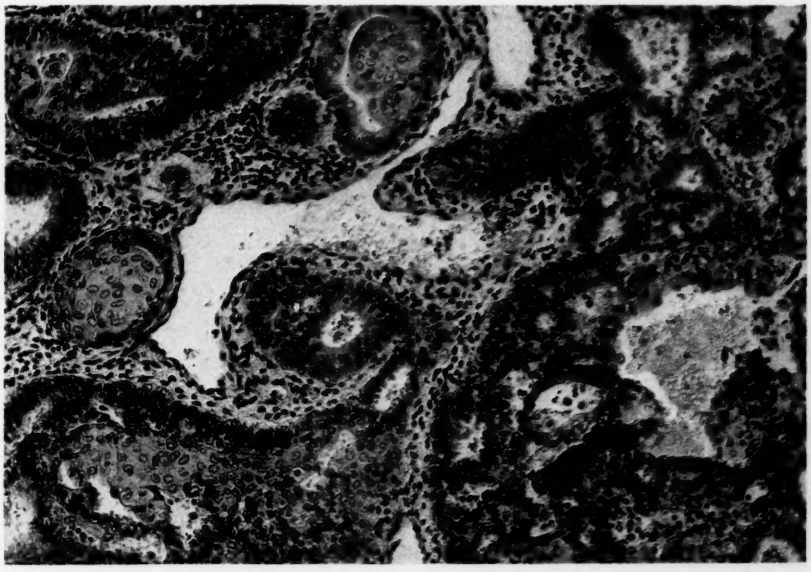

Fig. 1.—(33520.) High power photomicrograph of section from uterine curettings. Note how the squamous cells almost fill the lumen of several glands.

Microscopic examination (Dr. R. H. Friday):

"The uterine curettings show a marked hyperplasia of the glandular elements with loss of the normal pattern and secondary acinar formation. The cells lining the glands are three to four layers deep. They are pleomorphic and hyperchromatic, and in some areas form cordlike projections. There is quite extensive squamous cell metaplasia in some areas, giving the picture of adenoacanthoma.

"*Diagnosis:* Adenocarcinoma, Grade II, with squamous cell metaplasia."

Jan. 21, 1942: Under spinal anesthesia, the abdomen was opened in the midline. The uterus was normal in size, shape, and position, except for one small fibroid. What we had thought was a cornual fibroid proved to be the left ovary which was cystic in part and also demonstrated a hard indurated portion with macular projections from its surface. A radical panhysterectomy and bilateral salpingo-oophorectomy were done. The iliac vessels were exposed and a search made for lymph

nodes; none were found. The patient made an uneventful recovery and was discharged from the hospital on her twelfth postoperative day.

Feb. 16, 1942: First follow-up visit revealed nothing of note.

Pathologic Report (Dr. Friday).—"Gross description: The specimen consists of a uterus with attached cervix, both tubes and ovaries. The

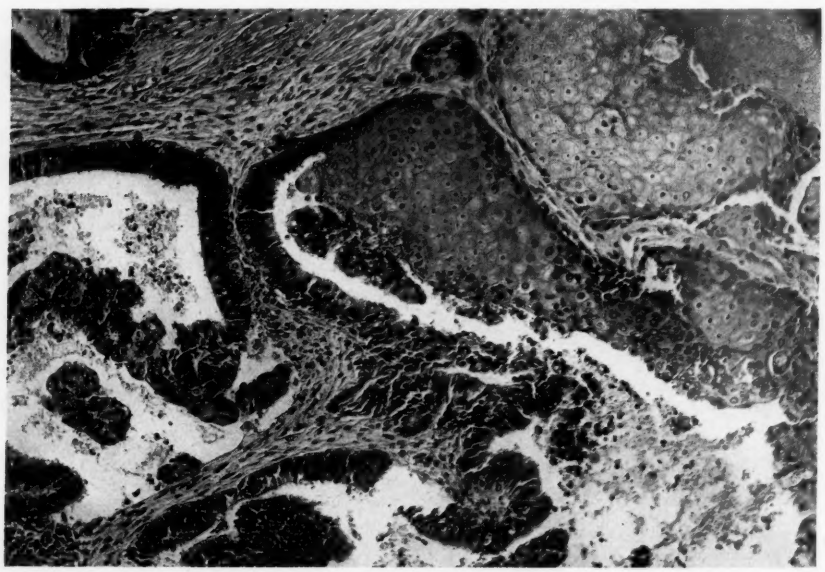

Fig. 2.—(33544.) High power. Section taken from the left ovary, showing adenocarcinoma and squamous epithelium which is highly differentiated into the adult type.

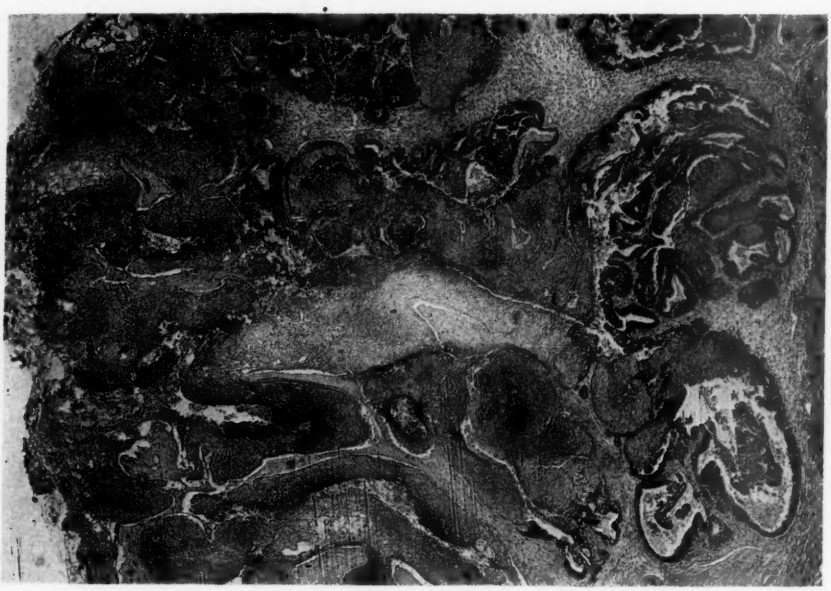

Fig. 3.—(33544.) Low power. Section from the left ovary demonstrating the marked keratin formation.

uterus is 6 by 8 cm. Its contour is smooth, except for a small fibroid tumor in the fundal wall. The myometrium is 1 cm. thick. The endometrium is shaggy, granular and hemorrhagic, and thickest at the fundic portion. The growth of endometrium extends to the internal os. The cervix appears normal. The left ovary is cystic and measures 4 cm. in diameter. On the surface there is a small cauliflowerlike projection which feels like keratin. The cyst lining contains several macular projections of similar appearance. The opposite ovary is small and sclerotic. The tubes are grossly normal.

"*Microscopic Examination.*—The sections through the endometrium showed a similar picture as the curettings. There is malignant growth of the glands with invasion of the myometrium to the depth of 3 mm. There is piling up of the epithelium and acinar formation.

"The cervix shows a chronic inflammatory reaction. The predominating infiltrating cell is the lymphocyte. The sections from the left ovary present a curious picture of metastatic adenocarcinoma, with marked squamous cell metaplasia. There is stratification and keratin formation. There is invasion throughout the wall of the cyst. The cells have all the characteristics of malignancy.

"Sections from the left tube show a moderate lymphocytic infiltration and fibrosis of the wall. No tumor cells are visualized.

"*Diagnosis:* adenocarcinoma of corpus uteri; metastatic adenocarcinoma to left ovary; chronic salpingitis (mild)."

DISCUSSION

This case of adenocarcinoma of the fundus with squamous cell metaplasia is of interest for several reasons. First, that we have a fairly early, low-grade malignancy demonstrating ovarian metastases. Second, we have found only one other case (Schattenberg and Ziskind) where metaplasia spread to the ovary and produced keratin. Third, the hopeless prognosis this case would have, had we chosen to use only radiation as some clinics propose. Fourth, this case is in keeping with Novak's statement that squamous cell metaplasia occurs "in adenocarcinoma of the lesser degrees of malignancy."

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5123 Wayne Avenue

PREGNANCY FOLLOWING OPERATION FOR CONGENITAL ABSENCE OF VAGINA*

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CONGENITAL absence of the vagina is a rather rare condition. Duckett and Flynn are quoted by Word[1] as being able to find only five hundred such cases in the literature up to 1936, and Word says that about fifty cases have since been described. Other anomalies such as absence of uterus and adnexa and absence of one kidney or the presence of a horse-shoe kidney may be associated with the vaginal defect.

In a recent article Varino and Beacham[2] state that there have been recorded only two cases of unicornuate uterus with complete unilateral absence of broad and round ligaments, tube, ovary, ureter, and kidney of which one is theirs and the other was described by Dannreuther in 1923. The case that I am about to report is a third, which presents in addition to the other anomalies an absence of the left uterosacral ligament and the vagina. Probably because of the close connection of the embryologic development of the urinary with the genital system, anomalies of the two are frequently encountered together. One hundred and twenty cases of congenital absence of one kidney associated with a uterine anomaly are said to have been reported in the literature (Wharton[3]).

The present case is, as far as I am aware, unique in medical literature. It is that of a woman of twenty-one operated upon for congenital absence of the vagina, which was present in association with a unicornuate uterus and a congenital absence of left kidney and ureter, left tube, ovary, round ligament, broad ligament, and utero-sacral ligament. There was also an abdominal left ninth rib. Within a few weeks after operation for the construction of an artificial vagina she became pregnant and was delivered by cesarean section of a full-term living baby.

CASE REPORT

M. R. (History No. 4596), aged 21 years, white, married, was admitted to the Cambridge Hospital on March 3, 1940.

Present Illness.—From the age of sixteen years she had experienced crampy pains every two months, but had never menstruated. At the age of seventeen she had gone to a hospital but no pelvic examination was made. After her marriage three years ago, she had never had successful marital relations. One and one-half years after marriage, however, she began to notice a small amount of blood, apparently about a teaspoonful in amount, that came from the urethra with urination at the time of the regular pains which still appeared at intervals of eight weeks and lasted three to four days. The last episode of such bleeding from the urinary meatus was noted two months ago before her admission to the Cambridge Hos-

*Presented at a meeting of the Clinical Congress of the American College of Surgeons, Boston, November 6, 1941.

pital. The patient had no knowledge of any congenital defects in ancestors or siblings.

Physical Examination.—On examination the following points of interest were noted: The breasts showed normal development and there was a normal distribution of axillary and pubic hair. Over the heart, which was otherwise normal, could be heard a soft, blowing murmur at the apex, which was not transmitted. An abdominal rib (ninth) on the left side extended across the abdomen nearly to the midline. The liver, kidneys, and spleen were not felt. The external genitals were normal anteriorly with well-formed clitoris, external urinary meatus, and labia minora. No perineal body was present, and there was no vaginal orifice. On rectal examination the finger brought anteriorly came up against the urethra, with only the rectal wall intervening. The cervix was easily felt and the uterus found to be small but of normal size and consistency, in good position but somewhat to the right of the midline. Urine and blood examinations were negative.

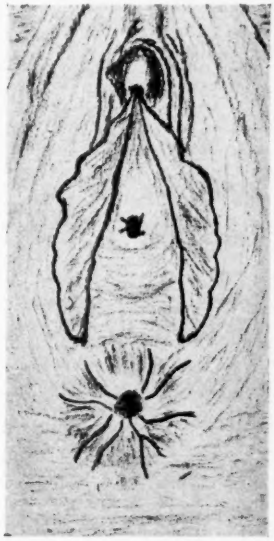

Fig. 1.—Drawing of congenital absence of vagina in Patient M. R.

Cystoscopy was performed by Dr. Harold Chamberlin on March 7, 1940. This examination revealed a normal bladder mucosa and a right ureteral orifice in the usual position. The right ureter was catheterized and a pyelogram made. The left ureteral orifice was not seen and the left angle of the trigone was noted as poorly defined.

Two days later the patient began to pass a slight amount of blood in the urine on voiding, representing her menstrual period. Urethroscopy and an intravenous urogram were made during the catamenia. Through the cystoscope several small reddened areas were seen in the trigone and bladder base but no bleeding from these areas was noted. On urethroscopic examination, moderate oozing of blood appeared to come from the urethral floor to the right of the midline, but no opening could be seen at this point. Pyelograms failed to demonstrate any kidney shadow on the left side and intravenous urograms confirmed this finding. On

the right side the shadow of the renal pelvis and the ureter and the kidney excretory function were normal.

Operation was performed on March 18 under cyclopropane, oxygen, and ether anesthesia. A No. 22 metal sound (F.) was first introduced into the bladder and held in the median line. With the left forefinger in the rectum, a two-inch transverse incision was made midway between the external urinary meatus and the anus. By blunt dissection with the finger, the bladder was carefully separated from the rectum, until the cervix was finally felt. Much bleeding was encountered in this stage of the procedure from the perirectal venous plexus. The artificial cavity thus created was enlarged laterally on both sides until the cervix with its external os was visualized and until the cavity would admit to its

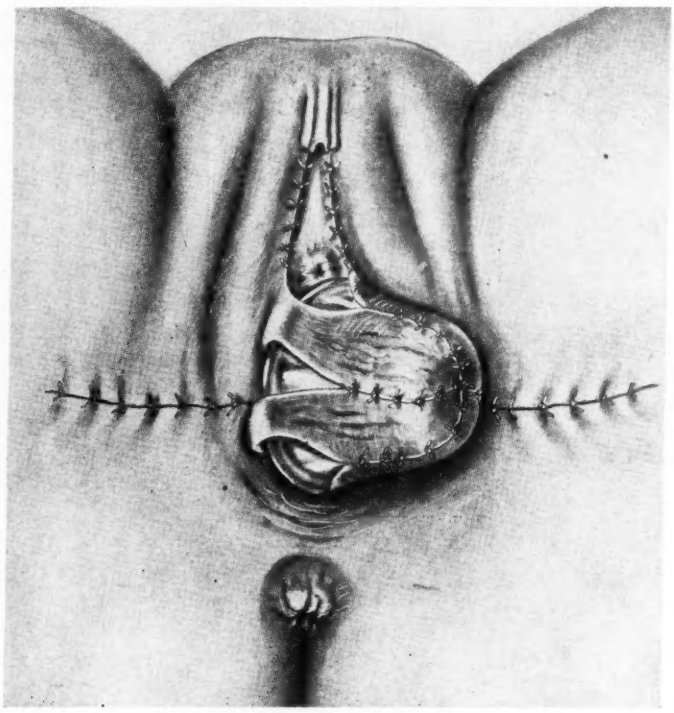

Fig. 2.—The Graves operation. (Reproduced from Graves *Gynecology* by courtesy of W. B. Saunders Company.)

full length a vaginal glass speculum 10 cm. (four inches) long and 3.8 cm. (1½ inches) in diameter. The cervix was then seized with tenaculum forceps and pulled downward more into range of vision. At this stage a fistulous tract was seen extending from the upper left side of the portio to the urinary bladder.

Four sutures of No. 1 chromic catgut were placed through the upper and lower quadrants of the cervix and left long. Four plastic flaps were next constructed to serve as a lining for the new vagina as follows: (a) Two flaps of mucous membrane were constructed by partially removing both labia minora beginning at the clitoris and dissecting them down to a point just above the orifices of Bartholin's glands, including a broad pedicle at the base of each flap. Each of these was

broadened out into a butterfly shape by incising the raw surface in its long diameter. (b) Then a flap was dissected from the inner aspect of each thigh consisting of the entire thickness of skin and subcutaneous fat. The four flaps were sutured together over an old-fashioned glass vaginal speculum as a form, thus constructing a tube with an orifice at its apex to fit about the cervix after the method devised by William P. Graves.[4] The four sutures of No. 1 chromic catgut which had been placed at the four quadrants of the cervix were threaded on a curved needle and brought through each of the four flaps near its apex. When these sutures were about to be tied, the glass form was removed and the entire tube was inverted, forming a lining for the artificially constructed vagina which was then packed with gauze overlaid with rubber dam.

Sterile dry dressing, pads, and T-binder and bandages were applied and a self-retaining catheter placed in the bladder. Since the patient had lost considerable blood from general oozing from the perirectal veins, she was given a transfusion following the operation.

The postoperative course was characterized by several minor complications, but the artificial vagina itself healed well. The pack was removed from the vagina on the second postoperative day. On the third day the catheter apparently became kinked and the dressing became saturated with urine. On the fourth day, since the hemoglobin was only 57 per cent and the red blood count three million, a second transfusion of 500 c.c. of blood was given. An oil retention enema and milk of magnesia by mouth were also given on this day. On the eleventh day the self-retaining catheter slipped out and the patient voided spontaneously.

The thigh wounds were noted as reddened as early as the third day, and by the seventh these began to gape. The left thigh flap had come out of the vagina and was partly necrotic. On the next day both thigh flaps had come out of the vagina and there was an increase in the purulent discharge. The perineal wound remained fairly clean and on the eleventh day the edges were approximated with adhesive bridge and the granulations sprayed with aristol powder. The labial flaps took well and on April 4 it was possible to insert a finger into the vagina and feel the cervix.

On April 5 under cyclopropane anesthesia a secondary closure of the thigh wounds was carried out. Granulating areas on the inner aspect of each thigh were curetted, the skin undermined above and below, and the skin edges freshened. Approximation of the edges was accomplished with pulley sutures and by plain interrupted sutures of heavy silk. This opportunity was also taken to dilate the artificial vagina.

The convalescence from the second operation was complicated by a left parotitis which developed on the fourth postoperative day. Sulfanilamide and x-ray treatment were given and the swelling disappeared in five or six days. The thigh wounds now healed satisfactorily and the patient was discharged on April 24, 1940.

As a result of my experience with this operation, I should in the future use only the labia minora to line the artificial vagina and not try to employ skin flaps from the thighs.

During the following six months the patient came to the office at bi-weekly intervals for dilatation of the artificial vagina. Coitus with normal orgasm was reported to have occurred five days after discharge from the hospital. Menstruation began on May 25 and lasted four days with a good, normal flow from the vagina. Although at first, following

the removal of the catheter in the hospital, there had been occasional urinary incontinence, normal control of urine was now attained.

A definite menstrual period occurred on June 27, and a very slight flow on August 7 which lasted only two days. Morning vomiting occurred several times, and on September 19 the uterus was found to be definitely enlarged and lying to the right of the midline.

From this point pregnancy progressed normally with occasional symptoms of slight incontinence. On March 10, 1941, rectal examination showed the cervix to be one and one-half fingers dilated, but the patient was advised to enter the hospital for cesarean operation. She was admitted on March 18, 1941, just one year after the operation. The indications for an elective cesarean operation were the rather rigid, narrow artificial vagina, with congenital absence of the perineal body. There was also the question of the strength of the uterine wall because of the supposed absence of left adnexa and ligaments.

Cesarean section was carried out on March 19 under spinal anesthesia through a right paramedial incision. The right rectus muscle was retracted outward and the peritoneum opened without incident. The uterus was incised between stay sutures and the incision enlarged with bandage scissors. A normal child, weighing five pounds, nine ounces, was delivered by the breech, and an anteriorly placed placenta with membranes was removed. The uterus was closed with three layers of No. 2 chromic catgut.

The uterus was next delivered and examined. There was now noted complete absence of the left adnexa, the left round ligament and broad ligament, and the left uterosacral ligament. The right tube and ligaments were normal, but the right ovary was somewhat elongated and larger than usual. The condition was therefore a true uterus unicornis. Palpation revealed also an entire absence of the left kidney. The abdominal wall was closed in layers without drainage and the patient returned to bed. She made an uneventful recovery and was discharged with the baby, both in good condition, on April 3, 1941.

Following this operation, the catamenia occurred at regular intervals of thirty to thirty-three days and lasted three to five days with rarely slight pain for the first twenty-four hours. Urinary incontinence had disappeared. She menstruated for the last time on Sept. 3, 1941, and vomiting again appeared in the mornings. A vaginal examination on Nov. 15, 1941, showed an introitus that easily admitted one finger to its full length, the caliber of the vagina being about one and one-half fingers. The external meatus could not be seen because it was drawn up beneath the symphysis by slight contraction of the anterior vaginal wall, and there was no perineal body. The cervix was definitely softened. The uterus was up at a good angle but somewhat to the right of the median line and enlarged to the size of a two months' pregnancy.

One other case of pregnancy following the construction of an artificial vagina was found in the literature. Wagner's[5] case reported in 1923 followed a Schubert operation, and differs from mine in the very important respect that there was present a small but definite vaginal canal with an opening which allowed the passage of menstrual blood. In my case there was no external opening at all, the only avenue for the escape of menstrual blood being the fistula extending from the left side of the portio to the vesical floor. In my case the blood was evacuated only when the patient relaxed the vesical sphincter muscle to micturate. For this reason only, my patient did not develop hematometra.

SUMMARY

This is a report of a case of successful childbearing following an operation for the construction of an artificial vagina in a patient who presented the following anomalies: Agenesia of the vagina, left tube and ovary, left round ligament, left infundibulopelvic and left uterosacral ligaments, together with agenesia of left kidney and the presence of an abdominal ninth rib on the left side. In this case the Graves' operation for the construction of an artificial vagina was eminently successful, although a modification in the technique has been suggested. The patient is now pregnant for the second time.

It is very important in the aftercare of patients operated upon for vaginal agenesis to stretch the artificial vagina twice weekly for six months. If they are married they should have coitus twice weekly during this time. The tendency to contraction of the artificial vagina, however, is over at the end of six months.

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FIBROMA OF THE OVARY

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OVARIAN tumors are very often associated with ascites. In cases of ovarian fibroma, the ascites is sometimes accompanied by hydrothorax. This symptom complex was first described by Meigs and Cass[1] and since then has been known as "Meigs' Syndrome." In his original report Meigs stated that he had no adequate physiologic explanation for this phenomenon. Bomze and Kirschbaum[2] suggested that the ascites and pleural effusion may be the result of a low-grade cardiac decompensation in a patient who has a subclinical or compensated cardiac weakness in which the cardiac reserve is just sufficient to withstand the strain of the patient's activities. The added stress thrown on the heart by the pressure of the heavy ovarian fibroma, combined with its possible interference with pelvic and lower abdominal circulation, may be sufficient to produce the low-grade cardiac decompensation. This view does not account for the fact that often the tumor may be small, hardly sufficient to interfere with the circulation by virtue of its weight or size. Neither does it explain the fact that the mere removal of the tumor is sufficient to bring about the disappearance of all the fluid as well as the complete recovery of the patient without any treatment being directed toward the cardiovascular system.

It would seem that the accumulation of fluid in the abdominal and thoracic cavities of patients with ovarian fibroma is not due to any

interference with the circulation but possibly to a disturbance in the water metabolism. This opinion is substantiated by the case reported here, where, in the presence of a very large ovarian fibroma, there was a fair amount of fluid in the peritoneal cavity as well as a marked subcutaneous edema confined only to the region of the lower abdomen. There was no edema of the lower extremities and no evidence of hydrothorax. In the absence of any evidence of cardiovascular pathology, a localized edema of such nature may be due to some disturbance in the water balance of the system.

CASE REPORT

P. S., a 41-year-old colored female, was admitted to the Beth Moses Hospital on March 4, 1941, with a history of irregular vaginal bleeding, weakness, and loss of weight. Two years ago her menstrual period, which was on time, lasted for twelve days instead of the usual five days; it was very profuse and was accompanied by passage of clots. She was admitted to the Kings County Hospital, Brooklyn, where she was told that she had a tumor. When the bleeding ceased, she signed a release. Three months later the patient had another episode of bleeding with passage of clots, lasting for one week. Since that time she has menstruated about every two months, the flow lasting from seven to eight days; it was very profuse with passage of clots. There was no dysmenorrhea. Three weeks prior to admission she felt dizzy and developed a slight cough. One day later she had a watery vaginal discharge. Eight days later she began to bleed profusely, the bleeding persisting until admission to the hospital. The patient was a gravida ix, para vi. She had had three miscarriages following the birth of her first child. Her youngest child was thirteen years old. The patient's menses started at the age of 13, occurred every thirty days, and lasted for five days. There was no dysmenorrhea or leucorrhea. The patient was suffering from constipation, her appetite was poor, and she had lost 80 pounds during the past year.

Physical examination revealed an acutely ill woman, cachectic and pale. Her blood pressure was 138 systolic and 76 diastolic. Heart examination revealed essentially negative findings. The lungs revealed the breath sounds clear. There were no râles or evidence of any fluid in the thoracic cavity. Abdominal examination revealed a visible and palpable mass filling the entire abdomen from the symphysis to the ensiform. The mass was slightly movable, hard, nodular, and not tender. The skin over the lower abdomen was leathery in consistency and edematous with marked pitting on pressure. There were dullness, anteriorly and tympany in the flanks. There was no evidence of shifting dullness. There was no edema of the legs. Vaginal examination revealed a multiparous outlet. The cervix was high in the vault of the vagina; it was lacerated, movable, and not tender. The uterus could not be felt independently of the abdominal mass. The adnexa could not be palpated. The general appearance of the patient, the anemia, the loss of weight, and the nodular feel of the abdominal mass suggested the presence of an ovarian malignancy.

Laboratory Findings.—Urine was essentially negative. Blood count revealed hemoglobin 6 Gm. per 100 c.c.; red blood count, 2,470,000; white blood count, 10,200; polynuclear leucocytes, 65 per cent; and lymphocytes, 35 per cent. Wassermann and Kahn tests were negative.

Blood chemistry revealed sugar 85 mg., urea nitrogen 8 mg., and chlorides 470 mg.

The patient received two transfusions of 500 c.c. each on the third and fifth days of her stay at the hospital. Her hemoglobin then rose to 9 Gm. per 100 c.c. and red blood count to 3,780,000.

Two days later a laparotomy was performed. At operation marked edema of the subcutaneous fat was found. There were about 500 c.c. of straw-colored fluid in the peritoneal cavity. The left ovarian tumor was the size of a basketball; it was twisted upon its pedicle and was solid in consistency, except for a few cystic areas. The uterus was slightly enlarged. The right ovary was solid, the size of a hen's egg. There was no evidence of any peritoneal or intestinal implantations.

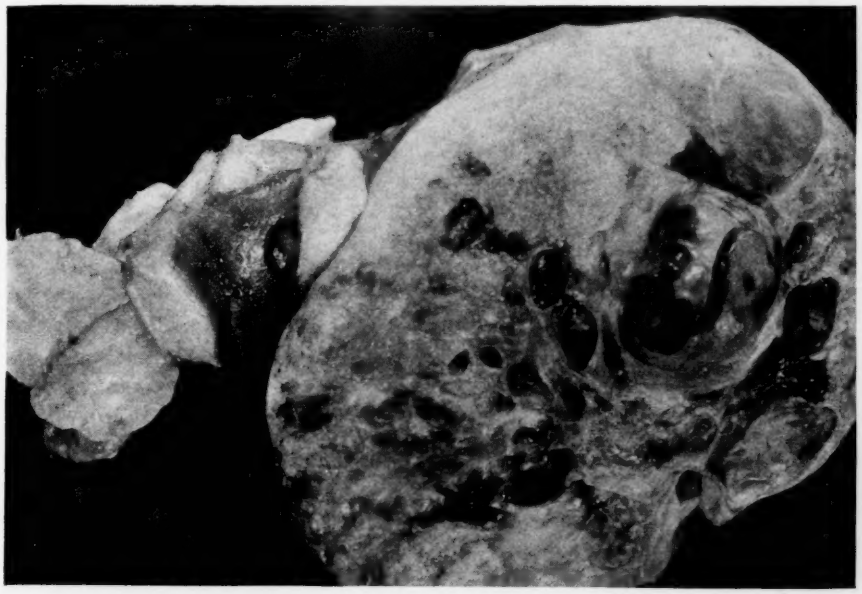

Fig. 1.—Cross section of left ovarian fibroma. Uterus opened, exposing endometrial cavity with small endometrial polyp. Cross section of right ovary.

In order to deliver the cyst, the abdominal incision had to be extended above and to the left of the umbilicus. The cyst ruptured at one point and some thick mucilaginous fluid escaped. A hysterectomy and bilateral salpingo-oophorectomy were performed.

The following is the pathologic report of the specimen, as described by Dr. A. R. Kantrowitz:

Gross: Specimen consisted of a supracervically amputated uterus, together with both tubes and ovaries. The uterus was regular in size, measuring 6.5 by 6 by 4.5 cm. The endometrial cavity measured 5 cm. in length. The endometrium presented a mottled hemorrhagic appearance. In the left posterior wall, 1 cm. from the fundus, there was a polypoid projection, 2 by 1 cm. The polypoid projection presented a mottled hemorrhagic appearance. The right tube measured 10 cm. in length; its fimbriated end was patent. The ovary measured 5.5 by 4 by 2.5 cm. It was firm in consistency and on cross section was found to

present a pearly-gray color with mottled yellow and tan areas. A cortical zone was rather well demarcated because of the presence of numerous 0.2 to 0.3 cm. sized grayish nodules. The left tube measured 15 cm. in length; its fimbriated end was also patent. A lappet of tissue, 5 by 3 by 2 cm., was adherent by tuboovarian ligament to the left tube. Contiguous with this mass, but demarcated from it somewhat, was a mass, 21 by 18 by 11 cm. This mass presented a smooth capsule. The surface vessels were distended and prominent and a number of bosses, representing the domes of cysts and containing clear to serohemorrhagic fluid, were noted. The remainder of the mass was solid except for innumerable spongelike areas presenting a reddish gray color. The solid portions of the mass presented a pearly gray color with circumscribed nodular areas and whorls of tissue resembling a fibromyoma of the uterus. The left ovarian mass weighed 2,270 Gm. without fluid evacuated and lost during the course of the operation.

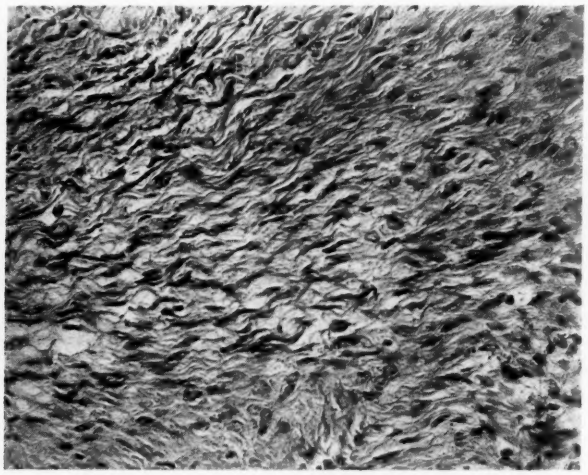

Fig. 2.—Microphotographs of ovarian fibroma, showing interlacing bundles of spindle cells.

Microscopic: The endometrium was in a stage of proliferation. The polyp was composed of endometrial stroma and glands. The tubes showed no essential changes. The right ovary showed a hyperplasia of the cortical layer. The mass in the left ovary was composed of interlacing bundles of spindle cells. There was no atypism. A rare mitotic figure was noted. Sudan stains revealed no fats. Doubly-refractile bodies were not found. The van Gieson and other fiber stains revealed only a collagen network of fibrils; no cytoplasmic network. Areas of degeneration and necrosis with cyst formation were noted. The lappet of left ovarian tissue was normal.

Diagnosis.—Large fibroma of the left ovary; hyperplastic right ovary; proliferating endometrium; Graafian follicle (left ovary); endometrial polyp.

The patient's postoperative stay in the hospital was longer than usual. There was a rise in her temperature to 103.4° F. on the third day. This lasted for three days, subsiding after sulfathiazole medication. The

condition was diagnosed radiographically as a right pneumonitis. The patient subsequently ran a subacute temperature from 100° to 100.2° F. due to an infection of the wound. This finally healed, and she was discharged from the hospital twenty-two days postoperatively in good condition.

SUMMARY

1. A case of large fibroma of the ovary is reported.

2. In addition to a small amount of fluid in the abdominal cavity, the patient had a marked localized edema of the subcutaneous tissue of the lower abdomen.

3. The possibility of fibroma of the ovary causing a disturbance in water metabolism is postulated.

4. Patient's history and clinical findings were strongly suggestive of malignancy. The value of surgery in cases thus diagnosed is once more emphasized.

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BILATERAL OVARIAN DERMOID CYSTS COMPLICATING PREGNANCY TREATED BY BILATERAL OOPHORECTOMY*

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FORTY-FOUR cases of bilateral dermoid cysts complicating pregnancy have been reported, of which 13 occurred during the first three months.

In 1938 Bernard Notes[1] of Washington, D. C., reported a case. He stated that a search of the literature revealed but 3 others.

In 1940 Andrews and others[2] of Norfolk, Va., reported a case and culled the literature to such an extent that they discovered 43 others, reports of some of which were incomplete. In this presentation, I wish to offer the forty-fifth and the fourteenth during the first trimester.

CASE REPORT

Mrs. E. C., a 25-year-old primigravida, first presented herself at the office on March 16, 1940. Her last period was Jan. 19, 1940, making her due, by dates, Oct. 26, 1940.

Her past history was negative. Her mother had died of intestinal cancer. Catamenia began at 12, occurred every thirty to thirty-five days with a scanty three-day flow, characterized by cramps and a bearing-down sensation premenstrually and on the first day of flow. Her last menstruation was a twenty-five-day interval period with the flow about half the usual amount.

*Presented at a meeting of the Obstetrical Society of Boston, January 20, 1942.
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She had the usual breast and urinary changes of early pregnancy. Nausea was constant and vomiting had occurred twice. There was occasional discomfort in the right lower abdomen.

Physical examination revealed a well-developed young female with findings consistent with pregnancy and with normal pelvic measurements. Hinton test and urine were negative. Blood pressure was 130/70. Usual and present weight was 132 pounds. The following findings were of interest: The patient had a moderate amount of black hair on her upper lip and chin; the arms and legs were unusually hirsute with male distribution upon the pubis. The uterus was boggy, retroverted, being felt in the pouch of Douglas, and a slightly tender egg-sized right adnexal mass was felt. A diagnosis of early uterine pregnancy and right ovarian cyst was made.

Two weeks later the patient was having considerable trouble with nausea and vomiting, she had lost four pounds, and acetone was present in her urine. Thiamin chloride and phenobarbital were administered. A week later her nausea and vomiting had improved, but she was having more frequent and severe pains in her lower abdomen. Examination revealed the ovarian cyst felt in the pouch of Douglas and it had increased in size.

On April 15, a month after her first visit, she reported with severe lower abdominal cramps (both sides) of two days' duration, "sore back," and constant pressure in the rectum. A mass could easily be palpated in the left lower quadrant. Rectal and vaginal examinations showed a grapefruit-sized mass blocking the pouch of Douglas; the pregnant uterus appeared to be anterior.

Laparotomy was performed the next day under ether, eighty-eight days after her last menstruation. A pregnant uterus of about three months' size presented. On the right side anteriorly was found a dermoid cyst about the size of a baseball, containing a large corpus luteum. This cyst was loosely twisted upon itself several times, but there were no signs of interference with the blood supply. Further exploration revealed a dermoid cyst of the left ovary, the size of a baseball, lying in the pouch of Douglas. Both tumors were excised at their pedicles, it being impossible to conserve any ovarian tissue. The patient made an uneventful recovery and continued her pregnancy. For financial reasons, no progesterone was administered. The pathologist reported bilateral dermoid cysts.

Fetal activity was noted during the first half of June. An attack of nervousness and rapid heart occurred during the seventh month. The last two months were characterized by pyelitis (first the right, then the left side), coryza, and sore throat.

Ten days from term the patient felt so uncomfortable from abdominal pains and recurrence of nausea that she was sent into the hospital for induction of labor. Her weight was only 136 pounds, a gain of 4 pounds.

Castor oil and quinine were administered, and since the head was deeply engaged, the membranes were ruptured. The cervix was not taken up or dilated (although rectal examination at home had seemed to indicate cervix well taken up). Within two days labor had not begun, whereupon several courses of pituitrin (minims 1) were administered at forty-five-minute intervals for several hours without results. Two ampoules of synthetic vitamin K were also given.

Four and one-half days elapsed before strong labor pains set in following a course of pituitrin. The pains were frequent and unusually severe. The cervix became 4½ fingers' dilated, but no more. Despite tetanic contractions, the head had not descended at all and remained L.O.P. in midpelvis. The fetal heart rose to 170, and the patient showed signs of exhaustion.

Accordingly an intravenous glucose administration was started, and on October 22, under ether anesthesia, delivery was accomplished by right mediolateral episiotomy, Dührssen's incision of cervix, manual rotation, and midforceps. The outer fibers of the sphincter ani muscle were lacerated during delivery and were sutured during the repair of the perineum. The male infant weighed 7 pounds 2 ounces and was 20 inches long. The puerperium was uneventful and afebrile with good healing of cervix and perineum. The supply of breast milk was plentiful, the baby weighing 3½ ounces over birth weight upon discharge on the fourteenth day. The mother nursed the baby until six weeks post partum at which time lactation was insufficient.

Six months post partum the patient experienced three days of typical menstrual flowing without pain. An endometrial biopsy was taken in the office which showed atrophic endometrium.* No cause could be demonstrated for the flowing. It had the appearance of menstrual discharge.

Eleven months post partum (September, 1941) she stated there had been no more vaginal bleeding. Hot flushes had been occasional up to the past week, since when they were severe. She felt nervous. Her weight had increased to 146 pounds. Phenobarbital in small doses was recommended.

In conclusion, information concerning the stage of pregnancy, treatment, and outcome of all 44 cases is not available. Andrews has assembled an interesting table in which bilateral oophorectomy was performed in pregnancy, irrespective of cause. Including this case, there are 14 described as performed during the first trimester; of these 11 carried on to term, 3 aborted.

SUMMARY

A case of bilateral dermoid cysts complicating pregnancy is presented in which bilateral oophorectomy was performed during the first trimester. The patient was delivered with difficulty at term of a live baby which she nursed for six weeks. Six months post partum menstrual-like bleeding occurred for three days. An endometrium biopsy taken at this time revealed an atrophic endometrium with no apparent cause for bleeding. There has been no recurrence. Otherwise the surgical menopause has been typical.

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*The endometrial biopsy was examined by A. T. Hertig, M.D., pathologist for the Boston Lying-in Hospital.

PRIMARY OVARIAN PREGNANCY

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ALTHOUGH the number of cases of ovarian pregnancies reported in recent years has increased greatly, the occurrence is still rare enough to warrant the reporting of every case.

We wish to report here what we believe to be a case of true primary ovarian pregnancy. It is generally considered that the pregnancy is of short duration and the early death of the embryo is due to hemorrhage with a rapid degeneration of the embryo. Spears[1] has stated that "the most usual course of ovarian pregnancy is an early ovarian abortion. This is followed by slight or severe intraperitoneal hemorrhage. The embryo is rarely found in these ovarian abortions, but chorionic villi are." Our case is of greater interest because an intact embryo was seen within the ovarian hematoma cavity.

REPORT OF A CASE

Mrs. M. C., a 29-year-old American housewife, entered the Chester Hospital on the gynecologic service of one of us (W. B. E.) on March 10, 1941, with the complaints of dysmenorrhea and irregular menses of several months' duration. Her last normal menstrual period had been on Jan. 28, 1941, eight days late, and lasted her usual duration of eight days. One week later she again had some bloody show, passing several clots. Soon after this, under medical treatment, she ceased bleeding, but was advised to see one of us (W. B. E.) because of a retroverted uterus and what was thought to be a tumor on the uterus. At the time of her entry into the hospital, the patient was alert and resting comfortably in bed. The blood pressure was 150/90; heart and lungs were clear; the abdomen was flat, soft, and not tender; there was a questionable mass in the right lower quadrant extending toward right flank, and on vaginal examination a mass was found in the right adnexal region. The past history was nonessential. She had had three full-term pregnancies, one of the children having died.

Diagnosis.—Right ovarian cyst.

Laboratory data were not unusual and on March 12, 1941, she was operated upon under gas-ether anesthesia. The abdomen was opened through a midline incision. A pedunculated mass about the size of a fist was found replacing the right ovary, and this mass had gravitated into the cul-de-sac where it was adherent. The tumor mass was dissected free and removed along with the right tube which appeared grossly normal. The abdomen was closed in layers with one drain in the pelvis. The appendix was also removed.

Postoperative Diagnosis.—Right dermoid cyst.

PATHOLOGIC REPORT (DR. G. SICKEL)

Specimen consisted of a mass 7.5 by 7.5 by 4 cm. which was removed from the right adnexal region, and was accompanied by the right tube

*Deceased.

and appendix. The mass externally resembled the ovary, with a few cystic follicles projecting from the surface. The surface was rough where it had been adherent. On section it showed a large amount of blood clot and at the center a cavity 3.3 by 3 by 1.2 cm., in which there was a well-formed fetus about 1 cm. in length and estimated to be

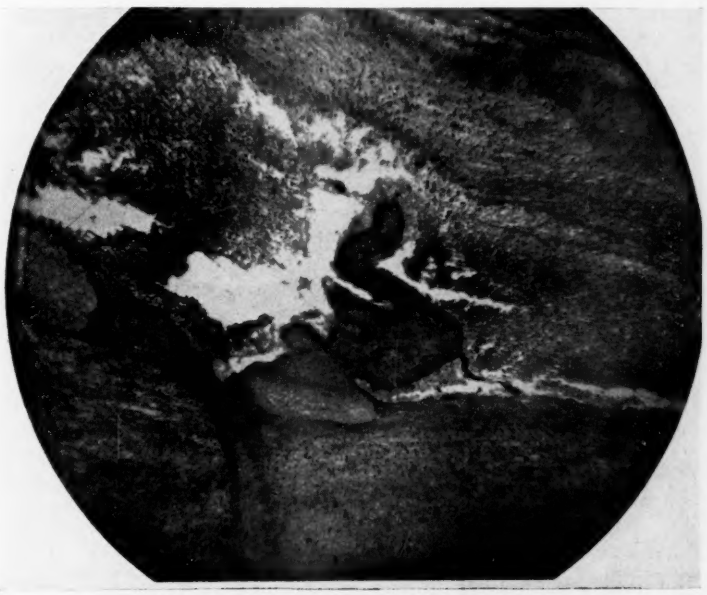

Fig. 1.—Section of ovarian hematoma showing chorionic villi.

Fig. 2.—Section of wall of ovarian pregnancy showing ovarian stroma; corpus albicans and cystic follicle.

about six weeks old. Along the periphery of the mass an old corpus luteum could be seen, but most of the mass was infiltrated with blood. The tube measured 5.5 cm. in length and had been removed in two pieces. The fimbriae were intact and open, and there was no evidence of a rupture in the tube. Microscopic sections consisted largely of blood clot with an area at the periphery which showed ovarian stroma and the remains of a corpus luteum and corpora albicantia. The tube was not sectioned. Within the sections of the blood clot were found a few chorionic villi.

CONCLUSIONS

This case is reported as an unusual case of primary ovarian pregnancy in which an embryo, estimated to be of about six weeks' gestation, was found intact within the ovarian hematoma. The case fulfills all the requirements as laid down by Spiegelberg, and although the tube was not serially sectioned, it appeared to be intact grossly. We present this as a case of true primary ovarian pregnancy, but its actual proof and the original distinction between primary and secondary types we leave as an open question.

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Since 1932, 229 cases of venereal lymphogranuloma were studied by the authors. A number of therapeutic procedures were employed and the best results were obtained following the use of sulfanilamide.

Ambulant patients were given the drug in comparatively small doses over a period of three to seventy-six weeks with intermittent rest periods. Hospitalized patients received larger doses for six to twenty-three days. The total amount of sulfanilamide administered to the inguinal cases varied between 37.8 and 82.8 Gm. and to the anorectal cases between 34.2 and 584.1 Gm.

Four of the inguinal cases were healed within three to six weeks after institution of treatment. The fifth case which was of nine months' duration was cured after sixteen weeks' therapy.

Of the anorectal cases, 11 (39 per cent) were completely healed, the same number markedly improved, 4 improved, and 2 remained unimproved. Fibrous strictures of the rectum were uninfluenced by treatment. There was a higher percentage of cures among the anorectal cases without than with rectal strictures. It is reasonable to consider, however, that the presence of stricture necessitates longer and more vigorous treatment than that given in this study. Rapid healing of the anorectal cases was more likely to occur when treatment was initiated early in the disease.

In the authors' opinion, sulfanilamide is a valuable agent in the treatment of venereal lymphogranuloma.

J. P. GREENHILL.

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

TREATMENT OF BLEEDING IN THE FIRST AND THIRD TRIMESTERS OF PREGNANCY

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(From the Department of Obstetrics and Gynecology, Cornell University Medical College and The New York Hospital)

VAGINAL bleeding in pregnancy must not be regarded as normal. In the first trimester, abortion and ectopic pregnancy are common causes, and require careful differentiation from each other. Bleeding is infrequent in the second trimester, and when it occurs, it is associated with either the causes of bleeding in the first and third trimesters, or with hydatidiform mole. In the third trimester, placenta previa, premature separation of the normally implanted placenta, and partial separation of a low-lying placenta are the main causes of vaginal bleeding.

BLEEDING IN THE FIRST TRIMESTER

This is of rather frequent occurrence, often requiring hospitalization. Of 24,289 pregnancies on the indoor service, 2,209 patients, or 9.0 per cent, were admitted to our clinic for treatment of bleeding.

The causes of bleeding in this group of patients is shown in Table I. Complete and incomplete abortion, threatened abortion, and ectopic preg-

TABLE I. CAUSES OF BLEEDING IN THE FIRST TRIMESTER OF PREGNANCY INDOOR SERVICE OF THE LYING-IN HOSPITAL, SEPT. 1, 1932, TO DEC. 31, 1940

	TOTAL CASES
Abortion, complete, or incomplete	1,648
Threatened abortion	229
Undetermined	185
Ectopic pregnancy	85
Hydatidiform mole	33
Erosion or polyp	18
Myoma	5
Chorionepithelioma	4
Carcinoma of cervix	2
Total	2,209
Total number of pregnancies studied	24,289
Incidence of bleeding in first trimester	9.0 per cent

nancy constitute the majority of cases. These lesions, together with other important causes of bleeding are also shown diagrammatically in Fig. 1.

It is our practice to admit to the hospital patients with bleeding in the first trimester of pregnancy. Whether in the hospital or at home, bed rest is essential. A careful history is obtained, particularly with reference to previous interference. Blood is obtained for grouping, white count, and cross-matching, sedimentation rate, hemoglobin and cell volume, particularly if the bleeding has been excessive. A general physical examination is now performed; but vaginal examination is deferred in certain patients, especially those with obvious threatened or incomplete abortion, or infection. If the history suggests ectopic pregnancy,

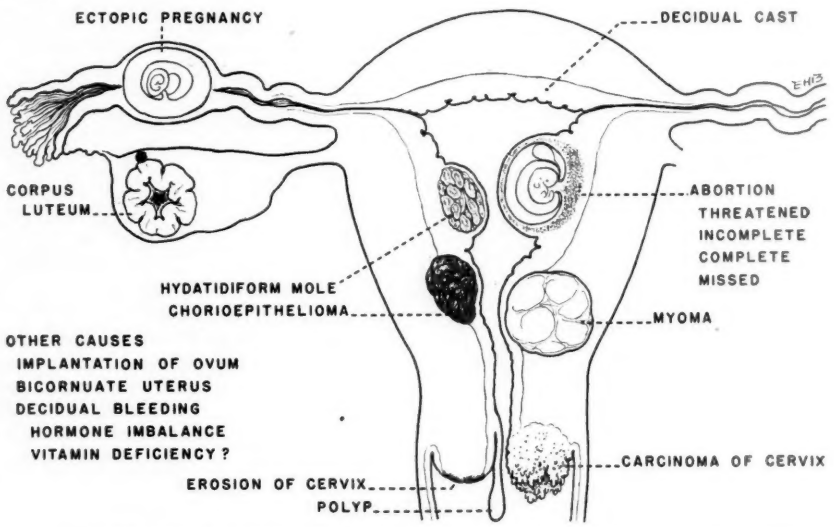

Fig. 1.—Diagrammatic scheme showing sources of ante-partum bleeding causes in first trimester.

vaginal examination is carried out. In other cases, a vaginal culture is taken. The temperature, pulse, and sedimentation rate and white count are observed for twenty-four to forty-eight hours unless excessive bleeding necessitates completion of the abortion.

Interruption of the pregnancy is performed on the basis of continued bleeding. In other patients, the fetus is expelled soon after observation is begun, and in these, operative intervention is often necessary, as shown in Table II. However, the abortion was completed spontaneously in nearly one-third of the cases.

TABLE II. OPERATIVE AND NONOPERATIVE TREATMENT IN INCOMPLETE ABORTION

Total number of cases	1,862
Spontaneous abortions, no curettage	602 or 32.3 per cent
Operative completion	1,260 or 67.6 per cent

Invasion of the uterus is avoided in febrile patients unless hemorrhage forces the issue. In these, intramuscular pituitrin, at times, has been of value in expression of the products of conception. Certain of these cases have shown the beta hemolytic streptococcus on vaginal culture, and in these chemotherapy has given good results. Recently, we have employed sulfadiazine in the treatment of these patients.

If a diagnosis of extrauterine pregnancy has been made, laparotomy is urgently indicated. Whole blood or plasma must be in readiness in all cases and given as indicated, usually during the laparotomy. Prompt laparotomy and blood transfusion, during and following operation, are the important factors in the treatment of women suffering from ruptured ectopic pregnancy. In a few instances, the patient's condition may be so desperate that transfusion should precede the operative procedure. This treatment, with particular emphasis on blood transfusion and prompt laparotomy, has been followed in our 85 consecutive patients with an extrauterine pregnancy and has resulted in a maternal mortality of 1 in 85, or 1.18 per cent.

Another group of patients with bleeding in the first trimester ceased bleeding after the preliminary twenty-four to forty-eight hours of observation. There were 439 patients in this group, of which 295 went to viability or term. Thus, 67.1 per cent were carried to viability or term, with a fetal mortality of 4.1 per cent. Congenital anomalies were not higher in this group. These patients were treated with bed rest, vitamin E, progesterone, thyroid, and other measures, and for the most part received no specific consideration on which to judge the results. Nevertheless, the end results compare favorably with those who use only progesterone or vitamin E, or some other therapy. This raises a serious question as to the efficacy of specific therapy unless a deficiency has been demonstrated.

Moreover, there are other causes of bleeding, as shown in Table I. For example, cervical erosion and polyp may be the cause of the bleeding, and not a threatened abortion. Naturally in these, specific therapy, using this or that hormone or vitamin will be credited with saving the pregnancy, when bleeding was due to another cause. Therefore, it is our practice to perform a sterile visual inspection of the cervix before the patient is discharged in order to detect other causes for the bleeding. Such examination disclosed carcinoma of the cervix in two cases. These were treated disregarding the pregnancy.

Further end results of our treatment of 439 cases of vaginal bleeding are shown in Table III. As can be seen, over two-thirds of the patients had a premature or full-term delivery. The abortion rate was about twice that of the clinic rate of 6.8 per cent, and premature delivery occurred two times as frequently as in the total clinic population. The fetal mortality was nearly the rate for the clinic. Of significance was the subsequent development of placenta previa in 2.9 per cent of these

patients, or six times the clinic incidence. This supports the view that placenta previa occasionally may be the cause of spontaneous abortion. On the other hand, premature separation of the placenta was not increased in this group of patients.

TABLE III. END RESULTS IN 439 PATIENTS HAVING ANTE-PARTUM BLEEDING IN THE FIRST TRIMESTER

	NUMBER	PERCENTAGE	CLINIC CONTROL FIGURE
Abortion	69	15.7	6.8
Premature delivery	29	6.6	2.7
Full-term delivery	266	60.5	89.3
Unknown—did not return, delivery elsewhere, or had induced abortion?	75	17.1	
Total	439	99.9	
Other complications:			
Placenta previa	13	2.9	0.52
Premature separation	2	0.4	0.36
Infantile mortality	18	4.1	3.5

BLEEDING IN THE THIRD TRIMESTER

Ante-partum hemorrhage in the last third of pregnancy is generally due to a partial or complete separation of the placenta from the uterine wall. When the placenta is implanted in the neighborhood of the internal os, we are dealing with the various types of placenta previa—centralis, lateralis or partialis, and marginalis. On the other hand, if the organ occupies its normal site in the upper portion of the uterus and separation occurs, we speak of premature separation of the normally implanted placenta. In addition to these two distinct entities, there is a group, in which diagnosis is often difficult to establish, comprising the cases of partial separation of a lowly implanted placenta. Inspection of the maternal surface of the placenta, immediately after its delivery, will often establish the diagnosis,.

TABLE IV. CAUSES OF ANTE-PARTUM BLEEDING IN THE THIRD TRIMESTER OF PREGNANCY (SEPT. 1, 1932, TO DEC. 31, 1941)

	CASES	INCIDENCE PER CENT
Placenta previa	134	0.52
Premature separation of the normally implanted placenta	93	0.36
Separation of placenta with low implantation Undiagnosed placenta previa Cervical lesions	334	1.3
Total	561	
Total number of term pregnancies	25,531	
Incidence of bleeding	2.19 per cent	

In our cases under discussion, bleeding during the third trimester occurred in 561 of 25,531 pregnancies reaching viability or term, an incidence of 2.19 per cent. A definite diagnosis of placenta previa was

made in 134 patients and premature separation of the normally implanted placenta in 93, giving an incidence of 0.5 per cent for the former and 0.36 per cent for the latter.

It is our practice to hospitalize every patient with bleeding in the last trimester of pregnancy. Upon admission, blood is obtained for grouping and cross-matching, and a suitable donor or blood in the Blood Bank procured. Hemoglobin and cell volume determinations are, of course, carried out. Thereafter, a careful history is obtained and physical examination made, the pulse and blood pressure being carefully noted. If there is no urgency, due to the patient's general condition or to excessive blood loss, she is observed for four or five days before vaginal examination is performed. If the patient is not at term, a longer period of time may be permitted to elapse. During this period of observation, the bleeding generally ceases, or the patient goes into labor and delivers spontaneously. On the other hand, persistent bleeding may necessitate earlier examination and intervention.

The sterile vaginal examination is performed in the operating room where everything is in readiness for transfusion, laparotomy, or conservative treatment, such as the introduction of a bag. The location of the placenta, the parity, age, and condition of the mother, the condition of the cervix, and the estimated size and condition of the offspring are the main factors to be taken into consideration in the decision as to method of treatment.

It is our practice, in general, to restrict cesarean section to patients with central placenta previa and to those with partial placenta previa with a cervix too rigid to permit easy introduction of a balloon. We place more emphasis on the condition of the cervix than on the degree of partial or incomplete placenta previa. In those patients with partial placenta previa in whom a balloon is used, it is of importance that a large-sized bag be introduced into the amniotic cavity after rupturing the membranes. If a bag is not available, as may happen at home, satisfactory results may be achieved by Braxton Hicks' bipolar version, provided extraction is not attempted before the cervix is fully dilated.

The above conservative and expectant treatment applies primarily to patients with placenta previa or with a placenta of low implantation. In the patient with separation of the normally implanted placenta, severely ill and in shock, immediate interference may be imperative; but, here also, the most important phase of proper treatment consists of the immediate procurement of suitable blood for transfusion.

Operative interference is frequently employed for both placenta previa and premature separation, as shown in Table V. However, certain cases in either group were permitted to deliver spontaneously. In others, a Voorhees bag was inserted, and in others, artificial rupture of the membranes sufficed to hasten delivery. Transfusions were given before and

TABLE V. COMPARISON OF THE MODE OF DELIVERY IN PLACENTA PREVIA AND PREMATURE SEPARATION OF THE NORMALLY IMPLANTED PLACENTA

	PLACENTA PREVIA PER CENT	PREMATURE SEPARATION PER CENT
Cesarean section	43.2	41.9
Spontaneous delivery	16.4	37.6
Version and extraction	15.6	1.0
Insertion of a bag	10.4	1.0
Breech extraction	6.7	9.6
Forceps and other operations	6.7	7.4
Undelivered (died)	0.7	1.0

after delivery as was indicated. Packing of the cervical canal with gauze is never employed.

At times, the vaginal examination was not conclusive as to the cause of the bleeding, especially when the cervix is closed. In some of these, a cervical erosion was found on occasion, or a polyp, or a chronic cervicitis. These patients constitute an *undetermined* group, and in whom a low implantation of the placenta may also have been the cause of the bleeding. Patients in this group are sometimes permitted to go home, particularly when placenta previa has been ruled out. These patients often had an uneventful delivery, as shown in Table VI.

TABLE VI. MODE OF DELIVERY IN PATIENTS HAVING ANTE-PARTUM BLEEDING OF UNDETERMINED ORIGIN (COMPARE WITH TABLE V)

	NUMBER	PER CENT
Cesarean section	20	5.9
Spontaneous delivery	240	71.8
Operative delivery	74	22.2
Total	334	99.9

The maternal and fetal mortality in ante-partum bleeding in the third trimester are shown in Table VII, and indicate a marked increase when this complication of pregnancy is present. In placenta previa our maternal mortality was 0.75 per cent, and in premature separation of the normally implanted placenta 3.2 per cent.

TABLE VII. TOTAL MATERNAL AND FETAL MORTALITY IN ANTE-PARTUM BLEEDING IN THE THIRD TRIMESTER

GROUP	NO. OF CASES	MORTALITY			
		MATERNAL		FETAL	
		NO.	PER CENT	NO.	PER CENT
Placenta previa	134	1	0.75	31	23.1
Premature separation	93	3	3.2	49	52.6
Separation of placenta with low implantation Undiagnosed placenta previa Cervical lesions	334	0	0	44	13.1
Total	561	4	0.71	124	22.1

It is to be noted that the maternal mortality in all our patients with ante-partum bleeding during the latter part of pregnancy is 0.71 per cent, or 7.1 per 1,000, as compared with the clinic figure of 1.98 per 1,000. The fetal mortality is very markedly increased over the clinic figure, due primarily to the high fetal death rate incident to premature separation of the normally implanted placenta (52.6 per cent). The fetal mortality in placenta previa is 23.1 per cent. This latter figure may be somewhat reduced by the wider use of cesarean section. However, we are opposed to such extension of abdominal delivery, because the majority of the infants are premature and of the added risk to the mother.

In certain patients with vaginal bleeding, a closed cervix prohibits diagnosis of placenta previa. If the patients are a month from term, they are usually kept in the hospital until delivery. This represents an expensive form of treatment which has been justified in terms of a lowered fetal and maternal mortality. However, any procedure which can reduce this expenditure deserves investigation. For this reason, we have employed the x-ray in order to locate the placental site. In a series of 94 patients studied, 71 had antepartum bleeding. The causes of the bleeding in these cases is shown in Table VIII.

TABLE VIII. CAUSES OF ANTE-PARTUM BLEEDING IN 71 CASES STUDIED RADIOGRAPHICALY

Cervicitis	6
Placenta previa	12
Proved by operation or at delivery	
Low implantation	4
Undetermined	49
Total	71

Again, it is seen that a large number of patients fall into an undetermined group. However, placenta previa was diagnosed in 12 cases, all of which proved to be correct.

Location of the placental site by x-ray was advocated by Snow and Powell in 1934. About the same time Ude and Urner called attention to the diagnosis of placenta previa using contrast dye in the bladder. Our knowledge of the subject has been augmented by the reports of Snow and Rosensohn and of Brown and Dipple. It is our practice to take a lateral film, and if this fails to disclose the placental site, a frontal film is taken. Location of the placental site is sometimes difficult prior to the seventh month of gestation. In our series of 94 cases, of which 71 had ante-partum bleeding, the placental site was localized in all patients. Brown and Dipple were able to recognize the placenta in 85 per cent of their cases. In several of our cases, the pelvic bones obscured the placenta in the lateral film. In these, frontal films were of value in locating the placenta in the fundus or on the lateral wall.

As shown in Table IX, location of the placenta in the upper and lower portions of the uterus was made on the bulk of the placental shadow in the film. Most of the placentas were located on the anterior or posterior wall of the uterus, with 52 per cent on the anterior wall and

TABLE IX. LOCATION OF THE PLACENTAL SITE IN ROENTGENOGRAMS OF 94 CASES

	UPPER UTERUS	LOWER UTERUS	TOTAL
Anterior wall	27	22	49
Posterior wall	38	2	40
Fundus	3	0	3
Lateral walls	2	0	2
Total	70	24	94

42 per cent on the posterior wall. In the collective anatomic material of Pinard and Varnier and Van Cauwenberghe, 51 per cent were on the posterior wall and 39 per cent on the anterior wall, and this indicates a reversal in the anatomic percentages when compared with the x-ray findings, as shown in Table X. It is to be recalled that most of our

TABLE X. COMPARISON OF THE PLACENTAL SITE IN RADIOGRAPHIC AND ANATOMIC MATERIAL

	PRESENT X-RAY STUDY		ANATOMIC MATERIAL OF PINARD AND VARNIER AND VAN CAUWENBERGHE	
	NO.	PER CENT	NO.	PER CENT
Anterior wall	49	52	89	39
Posterior wall	40	42	116	51
Fundus	3		1	
Lateral walls	2		20	
Total	94		226	

patients were selected for study because of ante-partum bleeding. It appears from the higher incidence of placental attachment to the anterior wall that bleeding is more prone to occur under such circumstances. This conclusion is supported in part by the fact that in 10 out of 12 cases of placenta previa, the placenta was on the anterior wall.

As so often happens in the course of clinical studies, other findings are made apart from the original scope of the investigation. It was of interest to analyze the mechanism of the third stage in 75 cases having vaginal delivery on whom the placental site had been located in roentgenograms. Previous writers on the subject have not correlated the mechanism of Schultze and Duncan with the placental site. This has been done in Table XI. It can be seen that the Schultze mechanism occurred most frequently when the placenta was situated in the fundus and on the posterior wall. The Duncan mechanism was observed when the placenta was situated on the anterior wall and in the lower uterine segment.

It seems apropos to discuss separation of the placenta in the light of this new evidence. It has been generally conceded that detachment of

TABLE XI. THE MECHANISM OF LABOR IN THE THIRD STAGE WITH REGARD TO LOCATION OF THE PLACENTAL SITE

	SCHULTZE	DUNCAN	TOTAL
Upper uterus	43 or 70.5 per cent	18 or 29.5 per cent	61 cases
Lower uterus	2 or 13.6 per cent	12 or 86.4 per cent	14 cases
Total			75 cases
Anterior wall	16 or 42.1 per cent	22 or 57.9 per cent	38 cases
Posterior wall	28 or 75.9 per cent	9 or 24.1 per cent	37 cases
Total			75 cases

the placenta occurs along Nitabuch's layer which acts as a perforated line between the placenta and the decidua vera. Festooning, shortening of the uterine muscle fibers, and contraction of the uterus serve to reduce the size of the placental site. Pinard and Varnier have shown that the uterine wall is thinner at the site of placental attachment. This view is also borne out by the specimens in Canton's *Atlas* and by Morton's specimen of an uterus with placenta previa. It can be assumed that the thicker portion of the uterus can exert greater contraction than the thinner placental site. Under such circumstances, placental separation is probably initiated in the peripheral circumference, spreading rapidly to the center as the musculature over the placental site begins to contract. Contraction of the uterine musculature "ligates" the vessels and sinuses so that the retroplacental hematoma is of very small or almost negligible size, which is a not infrequent clinical finding. This concept receives additional support from the cases of low implantation or marginal placenta previa having partial separation. Bleeding is a frequent phenomenon under such circumstances, probably because the placenta is attached in the noncontractile portion of the uterus.

A word of warning to the general practitioner, as well as to the specialist, may not be out of order. The vaginal pack or tamponade must not be used, because of its inability adequately to control bleeding and the danger of infection, even under the best sterile precautions. In the occasional instance one may be forced to use the vaginal pack, wholly as a temporary expedient to check bleeding sufficiently to allow transportation to a hospital. The manual or instrumental dilatation of the cervix in patients with bleeding near term is to be strongly condemned, because of the inevitable cervical and at times lower-uterine lacerations resulting from such a procedure.

SUMMARY

1. Bleeding during the first third of pregnancy occurred in about 10 per cent of all obstetric patients admitted to the New York Lying-in Hospital in the past ten-year period.

2. This bleeding was due mainly to abortion, complete or incomplete, or to threatened abortion.

3. Other causes of bleeding were: (a) ectopic pregnancy, (b) hydatidiform mole, (c) erosion of cervix or polyps, (d) chorionepithelioma, (e) carcinoma of the cervix.

4. The proper treatment for patients with bleeding of the first trimester includes hospitalization, bed rest, blood grouping and matching, and physical examination. Observation for a varying period of time is essential in threatened as well as incomplete abortion. Conservative treatment is recommended in the presence of potential or actual infection of the uterine cavity.

5. Vitamin E and perhaps progesterone are of value in certain cases of threatened abortion. A low basal metabolic rate must be corrected with proper thyroid therapy.

6. Dilatation and curettage are performed on the basis of continued or excessive bleeding in incomplete or threatened abortion. The Aschheim-Zondek test is of value in these cases.

7. Curettage is not performed in infected patients. Hemorrhage in these patients may necessitate evacuation of the uterus with the finger or ovum forceps, used with utmost care.

8. The treatment for ectopic pregnancy is laparotomy with adequate transfusion.

9. Cervical erosion, polyps, and carcinoma of the cervix, although infrequent causes of bleeding, must be ruled out by examination. If these are present, the appropriate therapy is applied. In carcinoma of the cervix, early treatment is essential and must be carried out irrespective of the gestation.

10. Bleeding of the last third of pregnancy is due usually to placenta previa or premature separation of the placenta.

11. The incidence of placenta previa was 0.52 per cent and of premature separation of the normally implanted placenta 0.36 per cent.

12. All patients with bleeding in the latter third of pregnancy must be hospitalized and a suitable donor or blood from a blood bank procured immediately.

13. In all these cases, except those in shock or with excessive bleeding, an observation period of several days is indicated.

14. Our treatment in placenta previa is conservative, including the introduction of a bag in certain cases, except in central placenta previa, or in partial placenta previa with a fairly closed, long, or rigid cervix. In this latter group cesarean section becomes the procedure of choice.

15. In premature separation of the normally implanted placenta, cesarean section is performed unless the cervix is partially dilated and early vaginal delivery may be expected.

16. Where cesarean section is performed for premature separation of the placenta, hysterectomy should be done only in those cases where great disintegration of the muscular wall of the uterus is present and the organ does not contract satisfactorily.

17. With the treatment as outlined above our maternal mortality from placenta previa was 0.75 per cent and from premature separation of the placenta 3.2 per cent. The maternal mortality in all patients with antepartum bleeding during the last trimester of pregnancy, including low implantation and undiagnosed placenta previa, was 0.71 per cent.

18. We do not advocate wider use of cesarean section in placenta previa on the basis that it will increase the number of living infants, for cesarean section still carries an appreciable maternal mortality due to infection and hemorrhage.

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Lazarus and Schifrin: An Unusual Case of Benign Multiple Chorionic Villi Implants in Peritoneal Cavity Accompanied by Hemoperitoneum, Ann. Surg. **115**: 93, 1942.

The macroscopic appearance of an extrauterine chorionepithelioma is that of a tumor resembling a hematoma, presenting no anatomic relationship to the site of a pre-existing placenta, located anywhere in the peritoneal cavity, portio vaginalis, broad ligament, or in the vagina. The normal chorionic villus differs from the chorionic villus of a chorionepithelioma in that the cells of the latter show a greater tendency to invade blood vessels and to cause vasodilatation of surrounding capillaries. Tumors vary widely in their content of Langhans' cells and syncytium. The sites of predilection of chorionepithelioma are the lungs, vagina, and vulva.

Uterine bleeding is the outstanding symptom of chorionepithelioma, and may appear during or after the termination of pregnancy. The author reports a case of extrauterine chorionic implants found during a laparotomy for acute surgical abdomen. They appeared as dark purplish spots over the surface of the tube and the peritoneum. The villi were benign abdominal implantations. Repeated Aschheim-Zondek tests were negative, and continuous observation of the patient showed her to be perfectly well.

WILLIAM BERMAN.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF MARCH 10, 1942

The following papers were presented:

Transplantation of Fascia for Relief of Urinary Stress Incontinence. By Albert H. Aldridge, M.D. (For original article, see page 398.)

Diffuse Luteinization of the Ovaries Associated With the Masculinization Syndrome. Joseph A. Gaines, M.D. (by invitation). (For original article, see page 975, June, 1942, issue.)

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF DECEMBER 4, 1941

The following papers were presented:

Adenocarcinoma of the Uterus Followed by Sarcoma. Dr. Isador Forman.

Hydatid Mole With a High Persistent Titer of Gonadotropic Hormone. Dr. Owen J. Toland. (For original article, see page 502.)

Vulvovaginitis in Childhood. Dr. Walter Susaman.

Maternal Syphilis in an Industrial Center. Dr. Chester Reynolds.

MEETING OF MARCH 5, 1942

Papers presented:

The Histopathologic Diagnosis of the Atypical Endometrium. Bernard Mann, David R. Meranze (by invitation), and Leib J. Golub. (For original article, see page 460.)

An Evaluation of the Various Types of Cesarean Section. Edward A. Schumann.

Some Nutritional Problems of Surgical Patients. I. S. Ravdin, (by invitation).

OBSTETRICAL SOCIETY OF BOSTON

MEETING OF JANUARY 20, 1942

The following case report was given:

Bilateral Ovarian Dermoid Cysts Complicating Pregnancy Treated by Bilateral Oophorectomy. Robert H. Goodwin, M.D. (For original article, see page 525.)

MEETING OF FEBRUARY 17, 1942

The following paper was presented (by invitation):

The Use and Potency of Synthetic Estrogens. Dr. J. P. Greenhill, Chicago, Ill. (For original article, see page 475.)

PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

MEETING OF APRIL 13, 1942

The following papers were presented:

Pseudomyxoma Peritonei. Dr. H. W. Erving (by invitation). (For original article, see page 492.)

Diabetes and Pregnancy. Dr. L. L. Pennock (by invitation).

Ward, George Gray: Benign Gynecologic Hemorrhages, J. A. M. A. **115:** 1625, 1940.

In 19,603 discharges at the Woman's Hospital, New York, severe hemorrhage occurred in 371 cases or nearly 2 per cent. The author reviews the results of the treatment of functional bleeding with such measures as progesterone, chorionic gonadotropin, moccasin snake venom, repeated curettage, radium (200 to 300 mg. hours), and testosterone propionate. He states that 600 mg. hours is within the danger zone of sterilization. In functional bleeding after the menopause, the most satisfactory treatment comprises adequate curettage to rule out possible malignant disease, and the intrauterine application of radium. A dose of 1,800 mg. hours radiation is an average amount to insure permanent stopping of the bleeding. The author prefers this to x-rays.

Myomas that do not invade or encroach upon the endometrium are not the cause of uterine bleeding. The bleeding in nonmyomatous and in myomatous uteri is identical in origin and it is hormonal. Bleeding from a fibroid uterus after the menopause is always to be considered of importance. It may arise from a necrotic submucous growth, sarcoma, or carcinoma. The author advocates surgical therapy as a general rule in bleeding myomatous uteri. During the childbearing age, conservative therapy is the treatment of choice. In the fifth decade irradiation is excellent for abnormal bleeding with associated small intramural growths. Radium is of no value in the postclimacteric fibroid with no bleeding. The author advises surgical treatment of adenomyosis. The most common cause of intra-abdominal hemorrhage is a ruptured ectopic pregnancy. Massive abdominal hemorrhage may result from a ruptured corpus luteum cyst. Among less frequent causes of vaginal bleeding are mentioned cervical erosions, senile vaginitis, hypertension, typhoid, pneumonia, chronic valvular disease, diabetes, hemophilia, scurvy, and syphilis.

WILLIAM BERMAN.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Menstruation

Lozner, Taylor and Taylor: The So-Called Coagulation Defect in Menstrual Blood, New England J. Med. 226: 481, 1942.

The fluidity of menstrual blood and its apparent failure to clot have been accepted as established facts with, however, little agreement as to their cause. These phenomena have been variously ascribed to the presence of an anticoagulant, to the absence of one or more factors concerned with blood coagulation and to changes in the circulating blood.

Carefully planned studies of these writers showed that menstrual blood is strikingly similar to defibrinated blood and serum in its behavior toward thrombin, prothrombin, and fibrinogen. These observations indicate that the fluidity of the menstrual blood is caused by the absence both of prothrombin and fibrinogen. This can only mean that the menstrual fluid is blood that has already clotted, and that there is no coagulation defect. Menstrual blood actually is a suspension of the formed elements of blood and tissue debris in serum.

HUGO EHRENFEST.

Langman, Louis, and Burr, H. S.: An Electrical Study of the Human Cervix Uteri, Anat. Rec. 82: 427, 1942.

Using a microvoltometer with one lead on the cervix, and the other on the ankle, more than 150 records from 8 women have been taken. In nine cycles the cervix became negative for twenty-four to forty-eight hours. The authors state that this shift is associated with ovulation, although in only one case did it occur on the fourteenth and the fifteenth day.

L. M. HELLMAN.

Greene, Raymond: Influence of Menstruation on Suspension Stability of Red Cells, Lancet 2: 556, 1941.

The red cell sedimentation rate was measured on every day of the menstrual cycles of 10 healthy women. The figures obtained showed that, contrary to general belief, there is no change in the suspension stability of erythrocytes characteristic of any phase of the cycle.

CARL P. HUBER.

Sammartino, R., and Herrera, R. G.: Evidence of the Persistence of the Utero-Ovarian Cycle in Various Gynecopathies, Rev. méd. latino-am. 25: 375, 1940.

In a well-illustrated article the authors present sections of ovarian and endometrial material from 100 operative cases. In each case parallel illustrations show the endometrium and the corpus hemorrhagicum or luteum of the current menstrual

cycle. The authors wish to show that despite the presence of pelvic pathology of many types, the cyclic activity of the uterus and of the ovary proceeds pretty much on schedule, unless the pathology present is extensive or destructive.

R. J. Weissman.

Nobecourt, Pierre: The Relationships Between the First Menstruation and the Clinical Onset of Tuberculosis, Presse méd., No. 48, 929, 1940.

The author compares the time of onset of menses between a group of nontuberculous girls and a group of tuberculous girls. There were 811 patients, aged 10 to 18 years, in the nontuberculous group. Among this group, 422 girls (52 per cent) had passed their menarche. The average age at the time of the appearance of the first period, in this group, was 13 years and 3 months.

There were 103 girls, aged 10 to 17 years, in the tuberculous group and 51 (49 per cent) had reported their menarche. The average age at the time of the first period, in the tuberculous group, was 13 years.

The author reports that the beginning of clinical tuberculosis among the 103 cases was: before the first menses in 33.3 per cent, following the menarche in 58.8 per cent, and simultaneous with the first menstruation in 7.8 per cent of the cases.

The percentage of positive skin tests took its first great increase during the fourteenth year and was followed by a slight increase over this finding during the fifteenth year.

The author concludes that one cannot generalize on the basis of statistical studies. Early menstruation does not necessarily imply susceptibility to tuberculosis. Rather other factors, such as hygiene, the rate of body growth, and environment, during this period of life furnish the background for the tuberculosis than does any relationship to the precocity of menstruation.

Clair E. Folsome.

Sevringhaus, E. L.: Menstrual Abnormalities of Adolescence, J. Pediat. 19: 319, 1941.

Adolescence is not a sudden event but a state of progressive development, continuing not always at the same rate of progress. Maturity in reproductive capacity is not evident until the second decade of life. In recording the state of development of the adolescent usually too much attention is given to obesity and weight which are relatively slightly influenced by gonadal hormones. The latter more definitely influence skeletal structure. Family history must be taken into account because growth and development tend to follow certain family and individual patterns.

Reduced gonadal function manifests itself in different ways and may, but not necessarily does, express itself in delayed menarche for which there are various other causes. The clinical pictures of hypogonadism and hypopituitarism are different but "increasingly we doubt that they are different diagnostic classifications. They merely are different aspects of the same type of thing." These different pictures vary from amenorrhea to menorrhagia, and in between lie wide variations in menstrual intervals and duration of flows. All these manifestations the author now considers as evidence of ovarian underactivity, if they are due to any endocrine disturbance whatever, though menorrhagia or frequent flows still are considered by some as results of overfunction.

Biologic assays, if not done by an adequate laboratory, are worthless; they are of no value to the practicing physician at the present state of methods of study. Failure of complete development of secondary physical characteristics points to an endocrine background but diagnosis depends upon unmistakable evidence of under-

function in the primary genital tissues themselves. This demands tissue study of endometrium and vaginal mucosa. Only the latter, in the young girl, is more readily available for investigation through aspiration of vaginal desquamation discharge.

Endocrinologists have hoped to find a cure for dysmenorrheas. "None of the honest endocrinologists that I know about think they have anything like the answer to the dysmenorrhea question."

For the treatment of delayed or incomplete development of adolescence or of different aspects of hypogonadism estrogenic substances should not be used. They never stimulate development of the ovaries but in large doses, used for a long time, actually inhibit anterior pituitary activity and thus reduce ovarian function. We should want to employ gonadotropic anterior pituitary material but that commercially available for the last decade is far from satisfactory. Chorionic gonadotropin, extracted from the relatively cheap source of pregnancy urine, stimulates the ovaries of rabbits and rats but not those of the human female. Gonadotropic preparations from the serum of pregnant mares only recently have become available. They actually stimulate human ovaries. Improvement is being made in such preparations, but we still are in the stage of earliest and rather unsatisfactory development. "However our patients will not wait."

Thyroid has been overworked. It is really useful only if thyroid underfunction can be definitely established. In younger girls this cannot be done by means of the basal metabolic test. "If the serum cholesterol concentration is significantly increased, we have very good reason to suspect hypothyroidism." In jittery adolescent girls, thyroid may easily aggravate their nervousness. "Certainly the use of thyroid on an obese child who is not a hypothyroid is wasted."

"Precocious adolescence always appeals to me as a sort of tragedy, psychologically and sociologically." Most of these cases, contrary to prevailing views, are not connected with tumors of any structure, "but are due to increased activity of some of the normal mechanisms which bring on adolescence, presumably the anterior pituitary." Only with evidence of beginning adolescence with ages between two and four, maybe up to ten years, search for some beginning newgrowth should be made.

HUGO EHRENFEST.

Klingelhöfer, W.: Subsequent Fate of Girls With Juvenile Bleeding, Zentralbl. f. Gynäk. **65:** 743, 1941.

In the treatment of juvenile bleeding, the influence of extragenital disease, anatomic variations, polyps and avitaminosis must be considered. Most cases, however, have an associated disturbance of ovarian function. The author was interested in the subsequent fertility of these patients and found 15 women whom he could study after their climacteric.

All but 3 patients had no further signs of ovarian insufficiency after entering the third decade of life. None had attempted to prevent pregnancy, but of the group 4 were sterile, 1 had aborted, 3 had 1 living child without further pregnancies, 6 had 1 living child plus 1 or more abortions. Only 1 had more than 1 living child. The author concludes that the productivity of women having suffered from juvenile bleeding is subnormal.

R. J. WEISSMAN.

Vöge, A.: Therapy of Hemorrhage in Puberty, Zentralbl. f. Gynäk. 65: 254, 1941.

Vöge successfully treated 3 cases of juvenile glandular cystic hyperplasia of the endometrium by directing his efforts at producing a secretory mucosa. He administered gonadotropic hormone intravenously with the intention of converting per-

sistent follicles into corpora lutea. Subsequent curettings showed that one of the girls had an anovulatory cycle although all menstruated in a normal manner following the treatment.

R. J. WEISSMAN.

Pallos, K., and Treite, P.: The Pathology of Functional Uterine Bleeding in the Climacterium and Post Climacterium, Ztschr. f. Geburtsh. u. Gynäk. 122: 28, 1941.

This report presents a study of Robert Meyer's material from the Institute of Pathology of the First Frauenklinik in Berlin. The endometria were obtained because of uterine bleeding; 509 were from women 42 to 45 years old and included 8 carcinomas of the body of the uterus; 1,243 endometria were from women from 45 years of age to the menopause and included 32 endometrial carcinomas; 38 endometria were taken one-half to two years after the menopause and of these, 17 showed hyperplasia, 8 showed atrophy of the endometrium and 8 carcinoma of the body of the uterus. Of those which were taken more than two years after the menopause, 28 were diagnosed as hyperplasia, 84 as atrophy, and 96 as carcinoma of the body.

The so-called functional bleedings are then discussed at length (40 pages) with many photomicrographs included. Fifty per cent of the cases of functional bleeding during the preclimacterium showed irregular proliferation. In many others there was localized circumscribed hyperplasia. Of those endometria which showed functional (secretory) phase changes, 10 per cent were diagnosed as functional hypertrophy and in association with these, the author describes persistent corpora lutea or theca lutein cysts.

One hundred fifty-six endometria were obtained during menstruation and presumably because of abnormal bleeding. These are divided into the two groups: those from women of 42 to 45 years of age and 45 years of age to the menopause. These showed for the two groups, respectively, normal shedding in 9.6 per cent and 21.8 per cent, prolonged shedding 7.7 per cent and 16 per cent, and irregular shedding 15.4, and 29.5 per cent of the total 156 specimens.

No functioning (secretory phase) endometrium was found more than two years after the menopause and only four times in the period from one-half to two years after the menopause. It is concluded that a hyperplasia occurring naturally more than six years after the menopause justifies the diagnosis of an estrogen producing ovarian tumor.

Partial function (secretory phase) was found not infrequently in endometria showing hyperplasia. The author looks on this as evidence of the presence of a new corpus luteum formation occurring after prolonged hyperplasia.

The report includes much detailed clinical and histologic description of those more recently recognized endometrial disturbances. Too little attention has been given to these in this country and reading this report in the original is well worth while.

J. L. MCKELVEY.

Pignoli, Renato: Capillary Fragility in the Meno-Metrorrhagias and Its Changes Following Treatment With Ascorbic Acid, Ginecologia 7: 85, 1941.

In 56 patients with menometrorrhagia and 15 women with normal menstrual cycles the author first ascertained the capillary resistance with special techniques.

All these women received an intravenous dosage of 200 mg. of ascorbic acid. Twenty-four hours later repeat fragility studies showed that the capillary resistance remained at a linear level throughout most of the phases of the men-

strual cycles of normal women. There was a slight decrease in capillary resistance in the last few days of the old and on the first day of the new cycle.

In three cases of essential menometrorrhagia of puberty, the capillary resistance was noticeably lowered. Vitamin C promptly restored these values to normal.

In the adult women with menometrorrhagia the capillary resistance was found to be inconstant. Vitamin C produced no unusual or beneficial change in the capillary resistance.

Among the 20 patients with premenopausal menometrorrhagia the author observed a mild decrease in the capillary resistance prior to treatment with vitamin C. The vitamin did produce a slight increase in the capillary resistance but not to the degree seen in the pubertal group.

In 8 cases of hemorrhagic metropathies (Schroeder Type), the capillary fragility was consistently lower in the majority of the cases. All of this group responded favorably to vitamin C therapy.

The author concludes that ascorbic acid is effective in the treatment of the menometrorrhagias for these reasons: It acts directly upon the blood and increases its coagulability. It acts upon the capillary vessels by decreasing their fragility. Vitamin C may exert a luteinizing-like effect on the endometrium, possibly through some specific reaction with the progesterone.

CLAIR E. FOLSOME.

Kenny, Meave: Intravenous Use of Follicle-Stimulating Hormone of the Anterior Pituitary in Menstrual Disorders. Proc. Roy. Soc. Med. **34**: 804, 1941.

The author gives a detailed report of results in the treatment of menstrual disorders with intravenous injection of follicle-stimulating hormones extracted from pregnant mares' serum (Davis and Koff).

Out of 4 cases of metropathia hemorrhagica, 3 regular menstruations were induced. Two of them are definitely ovulating; in the third it is likely. The fourth case was a complete failure. One of the successful cases relapsed after thirteen months.

The preparation was of doubtful value in 2 cases of menorrhagia with ovulation, but there was definite clinical improvement. The flows became more regular and moderate in amount.

Only one of three instances of secondary amenorrhea showed satisfactory response. The patient is now menstruating regularly.

There has been noted a marked association of "psychic trauma" with onset of menstrual disturbances and relapse after apparent cure.

HUGO EHRENFEST.

Greenhill, J. P., and Freed, S. C.: The Electrolyte Therapy of Premenstrual Distress, J. A. M. A. **117**: 504, 1941.

The distressing symptoms consist of headaches, emotional instability, irritability, abdominal distention, nausea and vomiting, increased sex desire, pruritus and swelling of the vulva. The authors have postulated that under the influence of certain ovarian steroids, sodium is retained by the tissues with a subsequent increase in the extracellular fluid. They administered ammonium chloride for therapeutic purposes in order to prevent the retention of sodium in the tissues.

Ammonium chloride was given in doses of 3 Gm. daily divided into three doses starting ten to twelve days before the expected menstrual period. In order to limit the sodium intake, patients were asked to refrain from using table salt or sodium bicarbonate preparations. Out of 40 patients treated in this manner, 34 had definite relief from their symptoms.

Ammonium chloride is not specific in the electrolyte therapy of premenstrual distress or tension. Other salts which can withdraw or displace sodium can be equally effective.

WILLIAM BERMAN.

Sturgis, Somers H.: The Use of Stilbestrol in the Relief of Essential Dysmenorrhea, New England J. Med. 226: 371, 1942.

The author analyzes his results of relief of essential dysmenorrhea secured in the course of four years. By giving an estrogen in an early phase of the cycle in sufficient amounts he prevents an ovulation and secures an estrin withdrawal flow at the time of expected menstruation. This anovulatory pseudomenstrual flow obviously is painless. He readily admits certain difficulties in timing such bloody discharge properly and meets the possible argument of detrimental final effect on pituitary function through such systematic suppression of ovulation with the statement that in no case permanent cure of the dysmenorrhea so far has been achieved. If for any reason ovulation is not eliminated in the cycle a typical dysmenorrheic menstrual flow reappears. All that is gained is temporary relief, and for this purpose a 1 mg. dose of stilbestrol for twenty days equals the effect of six injections of 1.66 mg. of estradiol benzoate.

HUGO EHRENFEST.

Grossmann, L. L.: The Treatment of Delayed Menstruation With Prostigmin, West. J. Surg. **50**: 103, 1942.

The possibility of applying prostigmin therapy in certain types of delayed menstruation was first suggested in 1940 by Soskin, Wachtel, and Hechter (see Abst. in this JOURNAL **42**: 732, 1941).

Using prostigmin methylsulfate, intramuscularly, on 30 patients, Grossman was able to confirm both the results and conclusions advanced by the quoted writers. No toxic results were observed. Prostigmin is a valuable agent for precipitating the menstrual flow in cases of amenorrhea without definite organic background. This method deserves further study in regard to its possible aid in the early diagnosis of pregnancy.

HUGO EHRENFEST.

Halbrecht, J.: Placental Blood in the Treatment of Amenorrhea, Lancet **2**: 630, 1941.

A series of 34 patients who had had amenorrhea for periods ranging from four months to fifteen years received placental blood or plasma intravenously; 18 of them menstruated within five to thirty-five days after the end of the treatment.

Of 11 patients showing atrophy of the endometrium before treatment, 6 had a normal endometrium after 5 or 6 intravenous injections of 150 to 200 c.c. of placental blood or plasma.

CARL P. HUBER.

Stanca: Late Results in the Treatment of Amenorrhea by Means of Intra-Ovarian Injections of Hormone Preparations, Geburtsh. u. Frauenh. 2: 433, 1940.

In a number of patients with amenorrhea, Stanca injected ovarian preparations directly into the parenchyma of the ovaries. In half the cases success was obtained and in one case pregnancy resulted. In one patient who had epileptic attacks, these seizures stopped after therapy. The author maintains that this

treatment affects beneficially the internal secretion, not only of the ovaries but of the other endocrine glands.

J. P. GREENHILL.

Bennett, Michael J., and Russell, P. B., Jr.: Surgical Correction of Oligomenorrhea, Menorrhagia and Menopause by Ovarian Isoplastism, South. Surgeon 10: 154, 1941.

This report describes a method whereby certain contrasting types of ovarian dysfunction which have not responded to medication may be corrected by an exchange of ovarian grafts. In the first such corrective procedure which was performed in 1935, the results were successful; subtotal unilateral ovarian grafts were exchanged in two sisters who suffered, respectively, from menorrhagia and amenorrhea of functional origin. Upon the basis of the analysis of numerous case histories, and a correlated histologic study of tissues from the female generative tract, an anatomicoclinical classification was evolved. This was employed to serve as an aid in grouping patients. The two principal categories are: (1) Hyperinterstitial (hypofollicular), and (2) hypointerstitial (hyperfollicular). Complete study of the patients included blood chemistry determinations, biologic assays, and vaginal smears.

Three precautions must be observed preliminary to the performance of ovarian isograft: (1) The patients must be of the same blood group and cross-match satisfactorily; (2) the ovarian dysfunction must be complementary and of the same degree; (3) the tissues must be free of any transferable disease. The technique requires that the ovaries in both patients be simultaneously resected at the hilum with no attempts to secure hemostasis, and immersed in warm physiologic saline solution during the transfer. Coaptation of the transplant is accomplished by continuous suture with an atraumatic needle and No. 00 chromic catgut.

Eighty isoplastics have been performed with a negligible percentage of failure (0.8 per cent uncorrected), and with no deaths as a result of the procedure. The data of 40 of these cases are summarized in this paper. In no instance was supplementary hormone therapy required. Daily pre- and postoperative vaginal smears served to check objectively the results of this operative procedure. A viable graft was visualized at a cesarean section performed ten months later.

ARNOLD GOLDBERGER.

Siebke, H.: Menstruation Following Transplantation of Curettage Material in an Endometrium-Free Uterus, Zentralbl. f. Gynäk. 65: 1034, 1941.

The author refers to the work of other writers on operative attempts at inducing menstruation. A 32-year-old woman had caustic applications to the uterus three weeks post partum followed by six years of amenorrhea. Uterus and adnexa were normal to palpation, but the uterine cavity was found obliterated. The author curetted the patient's sister. On the fourteenth day of her cycle, and while preparing the patient's womb by reopening the cavity, he carefully planted into it bits of endometrium. Ten milligrams proluton were given at operation and daily for one week. Progynon, 50,000 I.U., was given on alternate days after operation for 6 doses. Morphine, 0.01 Gm., was given to minimize contractions. Eleven days after operation, corresponding to the twenty-fifth day of the donor's cycle, mild bleeding occurred. Seven normal menses had occurred up to time of writing. Stilbene was given to heighten proliferative activity prior to the third period.

R. J. WEISSMAN.

Announcement

A Registry of Ovarian Tumors

At its recent annual meeting the American Gynecological Society undertook the sponsorship of an *American Registry of Ovarian Tumors,* and appointed from its Fellows a committee of five gynecologic pathologists to carry on this work.

The need and wisdom of such a project must be obvious to every gynecologist, for no problem of pathology is in greater need of clarification. No entirely satisfactory classification of ovarian tumors exists, largely because of our ignorance of the histogenesis of many of these growths. Even in tumor types which are fairly well defined, such as the papillary growths, prognosis is often difficult, because of the not infrequent lack of parallelism between clinical and histologic malignancy, and mistakes in both diagnosis and prognosis are frequent. Again, tumors are not infrequently encountered concerning the nature of which even expert pathologists cannot be certain. Finally, a whole group of ovarian tumors of rather special histogenesis and histology has been described in recent years, and there are many pathologists who, because of the relative rarity of these tumors, have had no opportunity of familiarizing themselves with their histologic characteristics.

Instead of limiting its study to a registry of rare ovarian tumors, comparable perhaps to that which has been employed so successfully by general pathologists with bone sarcoma, the committee has decided to widen its scope to include ovarian tumors of all varieties. It therefore seeks the cooperation of all gynecologists and pathologists in this ambitious project, and appeals to them for cooperation by seeing to it that properly prepared slides of all ovarian tumors, more particularly those of unusual or doubtful nature, be sent to this central registry for composite study by the members of the committee.

With the slides should be sent an adequate clinical history, including such essential data as the patient's age, menstrual and marital history, gynecologic findings, and the operative procedure carried out, as well as a gross description of the tumor. Where photographs of the latter are available, they would be welcome. If the gross specimen or blocks of tissue are sent, they should be fixed in 10 per cent formalin.

It is obvious that the real value of such a study would be enormously lessened if it did not include also a study of the subsequent course of the patients, particularly in the malignant and doubtful groups of tumors. Such correlated clinical and histologic study must be the chief hope of improving our evaluation and classification of ovarian neoplasms. To facilitate such a follow-up study the name of the attending surgeon should be included in the data.

The Committee has no intention of making this a purely diagnostic service, but all those who send in slides will in due course receive reports of the diagnosis and classification arrived at by the Committee. Since each slide will be studied by every member of the Committee, and

perhaps by other pathologists as well, and since this will involve correspondence between men scattered in different sections of the country, it will be understood that such reports of findings cannot be made with great promptness.

Finally, the Committee fully appreciates that many of the ovarian tumors submitted to it will be worthy of report by the referring physicians, and it need scarcely emphasize that neither the Committee as a whole, nor any individual member thereof, will utilize any submitted case for publication without the express permission of the referring physician. It is hoped that, as the work progresses, reports of the Committee's studies will be published from time to time, but those referring cases for study will be given full credit in any such publication.

The Committee feels that it has been given a great opportunity to render a worth-while service and it sincerely hopes that individual clinicians and pathologists in all sections of the country will feel that they too can contribute vitally in this project, by developing the routine of sending slides of interesting ovarian tumors, with the above indicated data, to the committee for study and registry. This material should be mailed to Dr. Emil Novak, Laboratory of Gynecological Pathology, Johns Hopkins Hospital, Baltimore, Md.

EMIL NOVAK, CHAIRMAN
ROBERT MEYER
HERBERT F. TRAUT
GEORGE H. GARDNER
KARL MARTZLOFF

Item

American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 13, 1943, at 2 P.M. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held later in the year. All applications must be in the office of the Secretary by November 16, 1942.

Effective this year there will be only one general classification of candidates, all now being required to have been out of medical school not less than eight years, having in that time completed an approved one year general rotating interneship and at least three years of approved special formal training, or its equivalent, in the seven years following the interne year. This Board's requirements for internships and special training are similar to those of the American Medical Association since the Board and the A. M. A. are at present cooperating in a survey of acceptable institutions. All candidates must be full citizens of the United States or Canada before being eligible for admission to examinations.

All candidates will be required to take the Part I examination, which consists of a written examination and the submission of twenty-five (25) case history abstracts, and the Part II examination (oral-clinical and pathology examination). The Part I examination will be arranged so that the candidate may take it at or near his place of residence, while the Part II examination will be held late in May, 1943, in that city nearest to the largest group of applicants. Time and place of this latter will be announced later.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.